ORION-11

Inclisiran for subjects with ACSVD or ACSVD-risk equivalent and elevated low-density lipoprotein cholesterol

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On behalf of the ORION-11 investigators

ORION-11: Acknowledgements

Contributions from 7 countries at 70 sites

Country	Lead enrolling investigators		
Czech Republic	J Malecha	A Dufka	
Germany	M Licka	C Contzen	K Arelin
Hungary	K Nagi	C Hajdå	K Wittmann
Ukraine	R Stets	A Kulyk	H Myshanych
South Africa	N Fourie	E Van Nieuwenhuizen	
UK	N Sulli	Y Huong	M Blagden
Poland	A S-Bialynik	D Knychas	

ORION-11: Background and rationale

Challenges remain in ASCVD and risk equivalent patients

Since low density lipoprotein cholesterol (LDL-C) is cumulative and causal:

- Low lifelong levels are essential

For patients and practitioners:

- Interventions need to be safe, convenient and produce assured results

ORION-11: Background and rationale
Harnessing the natural process of RNAi

21-23mer double strand small interfering RNA

Anti-sense strand
Sense strand

Triantennary GalNAc conjugate

Small interfering double-stranded RNA

- Harnesses the natural process of RNAi
- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 specifically, durably and potently

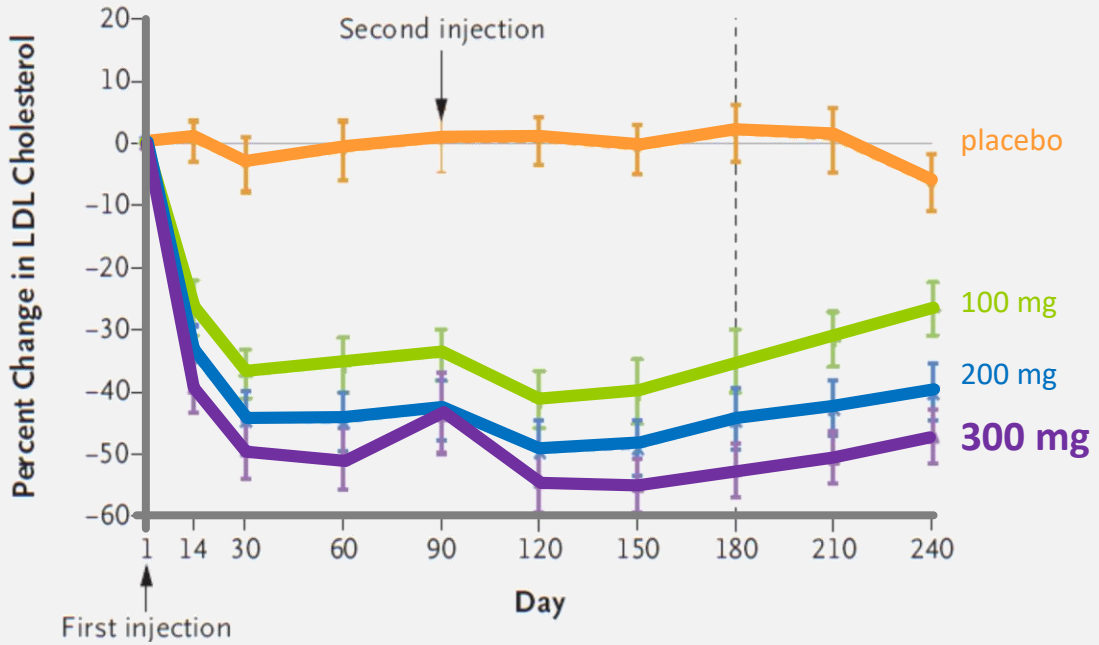
ORION-11: Background and rationale

Phase I-II inclisiran studies identified 2x/year dose potential

Dose-finding[1] and PD modeling[2] showed durable, potent effects on LDL-C

- 300mg led to 53% lowering of LDL-C
- Tested schedules gave durable responses
- PD models described effect-time course
- Extension studies affirmed long-term effect

Selected data from ORION-1 dose finding study



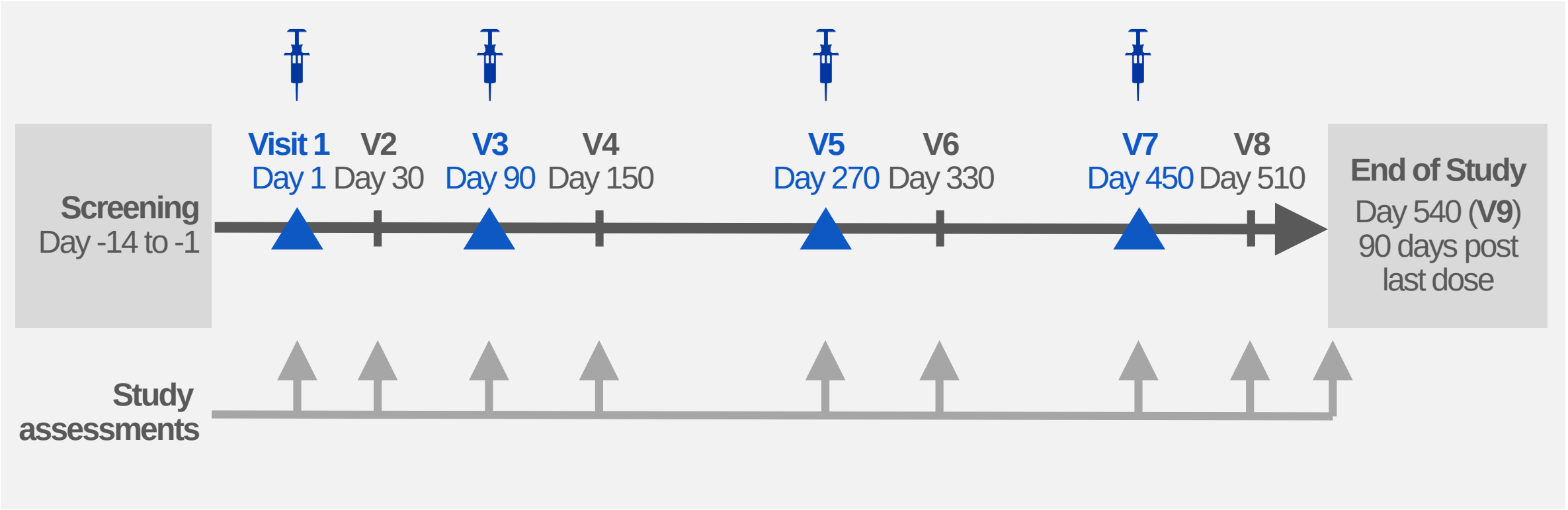
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2017;376:1430-40.

1. Ray et al. N Engl J Med 2017; 376: 1430-40 2. ORION-1 and ORION-3 presented at NLA Annual Meeting, Miami 2019 by JP Kastelein

ORION-11: Study design
Eighteen months treatment and observation

Randomized 1:1 inclisiran 300 mg *vs.* placebo – with maximally tolerated statins



ORION-11: Entry criteria
ASCVD and risk equivalent patients not at LDL-C goal

Inclusion criteria	Exclusion criteria
Age ≥18 years	Prior or planned use of PCSK9 mAbs
ASCVD or risk equivalent patients[1] • ASCVD LDL-C ≥70 mg/mL • Risk equivalent LDL-C ≥100 mg/mL	MACE within 3 months of randomization
	NYHA class III-IV HF — or LVEF 30%
Statin treatment Maximally tolerated doses Documented intolerance	Uncontrolled severe hypertension
	Severe concomitant non CV disease
Ezetimibe allowed	Prior/planned other investigational drug
Informed consent required	Fasting TG >4.52 mmol/L (400 mg/mL)

1. ASCVD-risk equivalents – comprising type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of ≥20% by Framingham Risk Score or equivalent that had a target LDL-C of <100 mg/dL.

ORION-11: Objectives
To confirm inclisiran efficacy and safety over 18 months

Study endpoints

1. Effectiveness

Primary

- Percent LDL-C change *vs.* placebo
  - At day 510
  - Average over days 90 – 540

Secondary

- LDL-C change over time
- Changes in PCSK9 and other lipids

2. Safety and tolerability

Treatment emergent adverse events

Laboratory parameters

3. Exploratory

Cardiovascular events[1]

1. MedDRA-defined cardiovascular basket of non-adjudicated terms including those classified within cardiac death, and any signs or symptoms of cardiac arrest, non-fatal MI and/or stroke

ORION-11: Statistical plan
Large sample enrolled to enable reliable inference

Sample size assumptions
- Mean LDL-C reduction will be no less than 30 mg/dL (SD 20 mg/dL) with 5% drop out rate
- >90% power to detect 30% lowering of LDL-C level with one-sided $\alpha = 0.025$

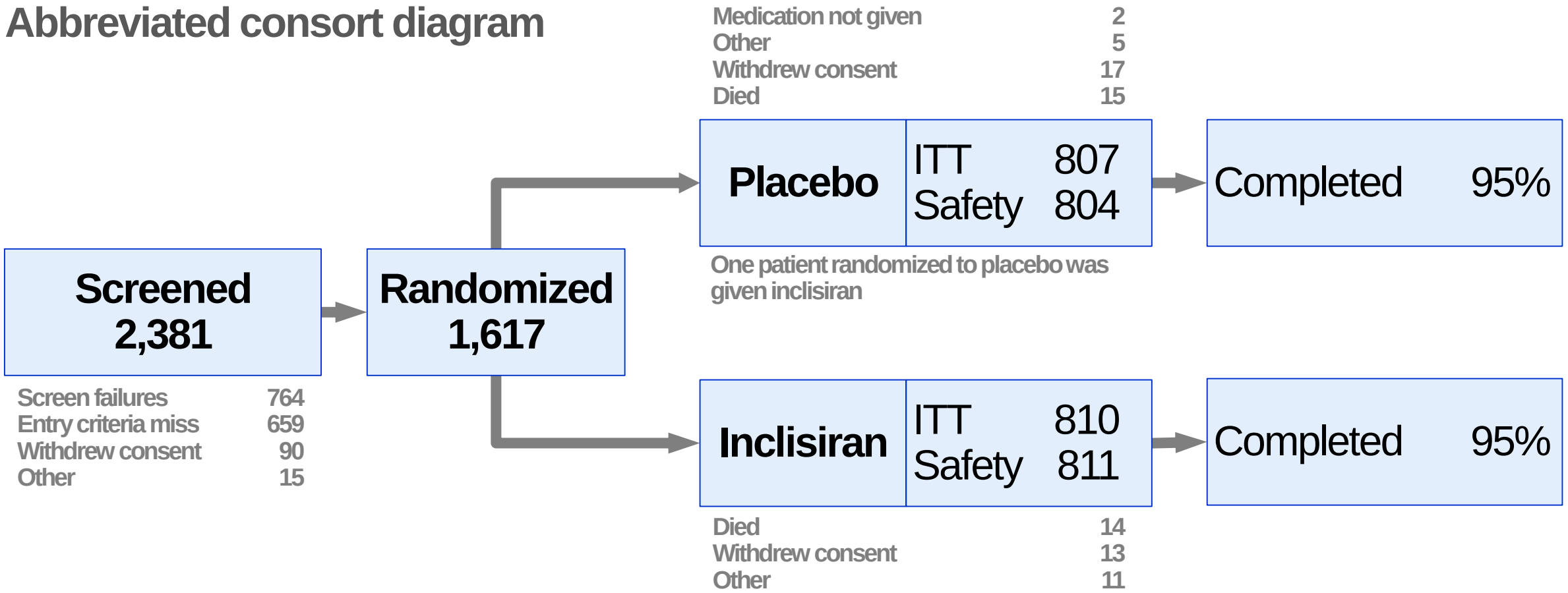
Primary endpoints
- Family-wise type I error rate controlled using a sequential testing procedure

Sensitivity analysis for primary efficacy endpoints
- Missing data assumptions will be assessed
- Pre-specified imputation and analysis methods will be used to account for missing data

Safety observation of ~3000 inclisiran injections and 1125 years patient exposure

ORION-11: Patient disposition
High proportion of patients completed 18 month study

Abbreviated consort diagram



1. Safety population comprises any subject given any study medication

ORION-11: Patients
Representative high risk cohort balanced by randomization

Patient characteristic	Placebo		Inclisiran	
ITT population[1]	N = 807		N = 810	
Age median (range) - years	65	(34-87)	66	(20-88)
Male gender	581	(72%)	579	(72%)
ASCVD	702	(87%)	712	(88%)
Risk equivalent	105	(13%)	98	(12%)
Statin use	766	(95%)	766	(95%)
Of which high intensity statins given	729	(95%)	734	(96%)
Ezetimibe use	62	(8%)	52	(6%)
Baseline LDL-C mg/dL (SEM)	104	(1)	107	(1)

1. All patients who were randomized, analyzed according to randomization 2. SEM is standard error of the mean

ORION-11

Efficacy results

Efficacy

Highly significant lowering of LDL-C relative to placebo

Treatment group	N (ITT)	Percent change LDL-C Mean at day 510	
		Observed	Imputed[1]
Placebo	807	+ 4	+ 4
Inclisiran	810	- 49	- 49
Difference (1º endpoint)		**- 54**	**- 53**
P-value		**<0.00001**	

1. Accounting for randomly missing values using mixed model repeated measures

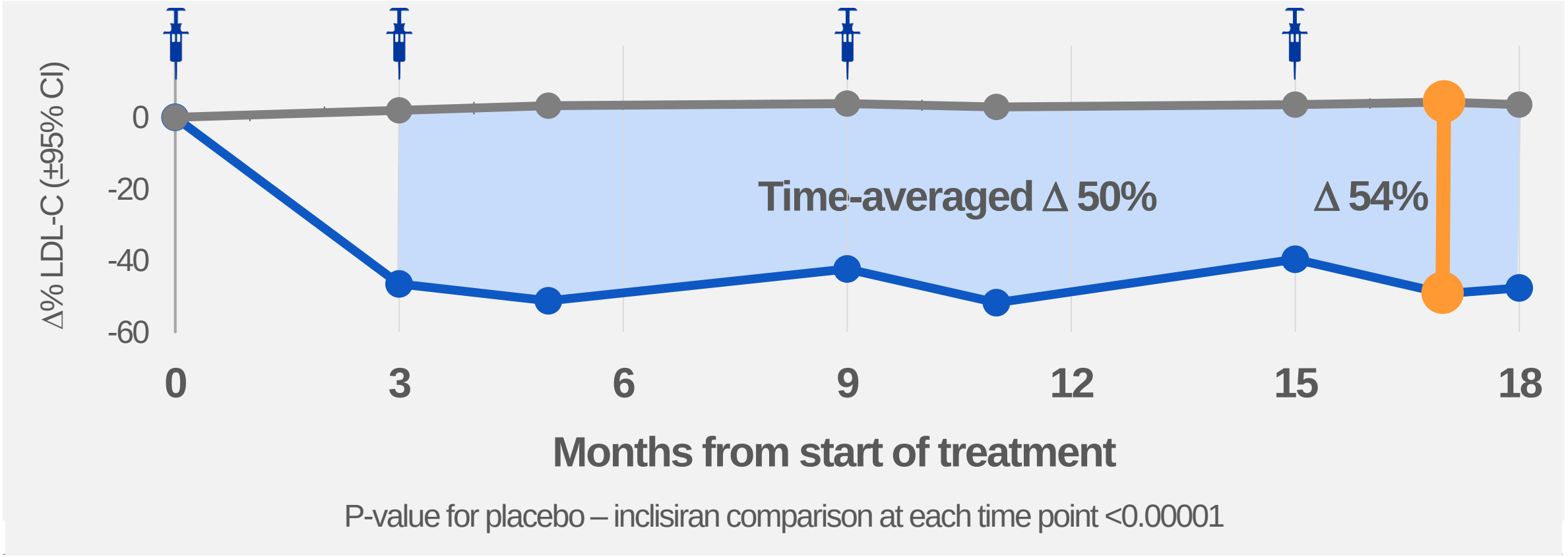
ORION-11: Efficacy
Highly significant lowering of LDL-C relative to placebo

Treatment group	N (ITT)	Percent change LDL-C			
		Mean at day 510		Time-averaged day 90 - 540	
		Observed	Imputed[1]	Observed	Imputed[1]
Placebo	807	+ 4	+ 4	+ 3	+ 3
Inclisiran	810	- 49	- 49	- 48	- 47
Difference (1º endpoint)		**- 54**	**- 53**	**- 50**	**- 50**
P-value		**<0.00001**		**<0.00001**	

1. Accounting for randomly missing values using mixed model repeated measures

ORION-11: Efficacy
Durable, potent and consistent effect over 18 months

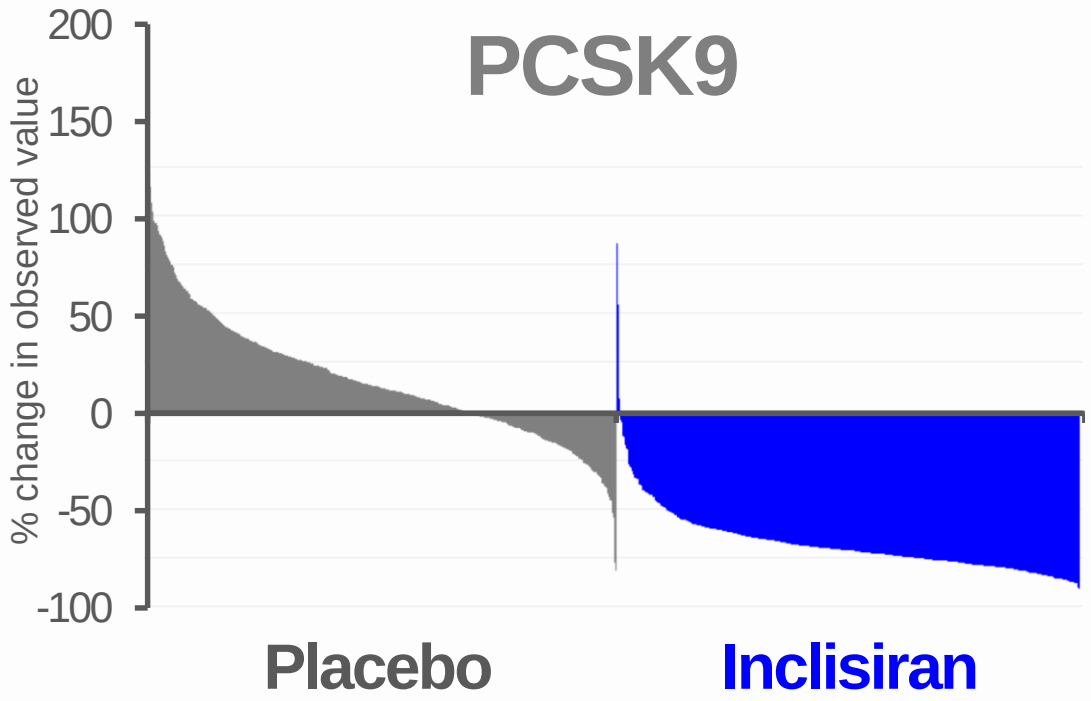
Percent change in LDL-C over time – observed values ITT patients

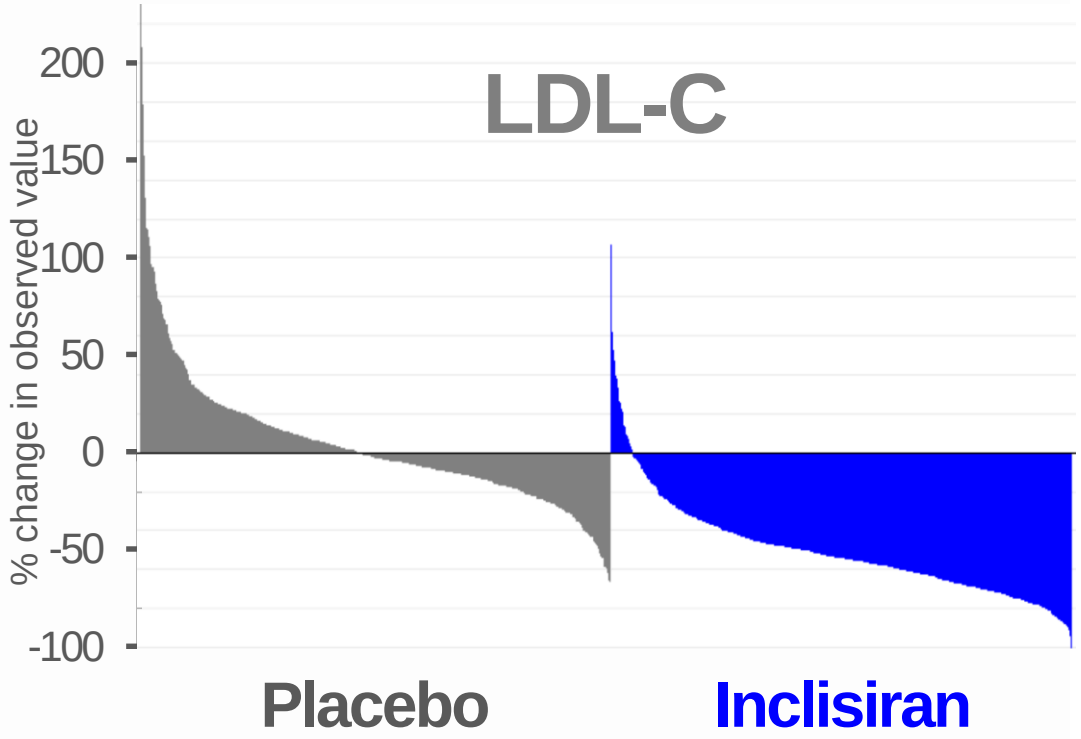


1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

ORION-11: Efficacy
Potent, consistent response to inclisiran

Individual patient responses contributing to primary endpoint -- 17 months





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Safety results

ORION-11: Safety and tolerability

Adverse event profile similar to placebo

Treatment emergent adverse event (TEAE) Safety population[1] – AEs in ≥5% patients	Placebo N = 807	Inclisiran N = 810
Patients with at least one TEAE	655 (82%)	671 (83%)
Diabetes mellitus adverse events	94 (12%)	88 (11%)
Nasopharyngitis	90 (11%)	91 (11%)
Hypertension	54 (7%)	53 (7%)
Upper respiratory tract infection	49 (6%)	52 (6%)
Arthralgia	32 (4%)	47 (6%)
Osteoarthritis	40 (5%)	32 (4%)

1. Safety population includes all patients who received at least 1 dose of study medication 2. Other TEAEs reported with lower frequencies than 5% in any group had no clinically meaningful differences

ORION-11: Safety and tolerability

Injection site AEs localized, mostly mild and transient

Injection site TEAEs Safety population[1]	Placebo N = 807		Inclisiran N = 810		Difference
Protocol-defined skin event	**4**	**(0.50%)**	**38**	**(4.69%)**	**4.19%**
(Reaction, erythema, rash, pruritus, hypersensitivity)					
Mild	3	(0.37%)	23	(2.84%)	2.46%
Moderate	1	(0.13%)	15	(1.85%)	1.73%
Severe	0	( )	0	( )	
Persistent	0	( )	0	( )	

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

ORION-11: Safety and tolerability

No evidence of liver, kidney, muscle or platelet toxicity

Laboratory tests Safety population[1,2]		Placebo N = 804		Inclisiran N = 811	
Liver function	ALT >3x ULN	4	(0.5%)	4	(0.5%)
	AST >3x ULN	4	(0.5%)	2	(0.2%)
	ALP >2x ULN	2	(0.2%)	1	(0.1%)
	Bilirubin >2x ULN[3]	8	(1.0%)	6	(0.7%)
Kidney function	Creatinine >2 mg/dL	11	(1.4%)	5	(0.6%)
Muscle	CK >5x ULN	9	(1.1%)	10	(1.2%)
Hematology	Platelet count <75x10^9/L	1	(0.1%)	0	(0.0%)

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 3. No cases met Hy's Law

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

ORION-11: Exploratory endpoint
Adverse cardiovascular events

Cardiovascular TEAEs Safety population[1,2]	Placebo N = 804		Inclisiran N = 811	
Pre-specified exploratory CV endpoint[3]	83	(10.3%)	63	(7.8%)
Cardiovascular death	10	(1.2%)	9	(1.1%)
Fatal or non-fatal MI and stroke[4]	30	(3.7%)	12	(1.5%)
Fatal or non-fatal MI	22	(2.7%)	10	(1.2%)
Fatal or non-fatal stroke	8	(1.0%)	2	(0.2%)

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. MedDRA-defined cardiovascular basket of non-adjudicated terms including those classified within cardiac death, and any signs or symptoms of cardiac arrest, non-fatal MI and/or stroke 4. Post hoc analysis of hard endpoints

ORION-11: Summary
Twice-a-year inclisiran lowered LDL-C by ≥50% safely

Efficacy
- ORION-11 met all primary and secondary endpoints
- Inclisiran reduced the primary LDL-C endpoint by 54% at 17 months, 50% time averaged
- Inclisiran resulted in potent, consistent PCSK9 knock down

Safety and tolerability
- Inclisiran safety profile was similar to placebo
- No adverse changes in laboratory markers
- Injection site events 4.2% - predominantly mild and none persistent

Exploratory endpoint
- Numerically fewer CV events were reported for inclisiran than placebo

ORION-11: Conclusions and implications

Inclisiran is the first cholesterol lowering siRNA

Inclisiran achieves durable and potent LDL-C reduction with only 2x yearly injection

Excellent safety profile in a high cardiovascular risk population

Administration by HCP potentially coincides with typical six-monthly patient visits

- Lends itself to routine clinical practice
- Enables provider control over medication adherence
- May offer patients meaningful new choices
- Offering safe, convenient and assured results