ORION-9

Inclisiran for heterozygous familial hypercholesterolemia

FJ Raal Johannesburg

D Kallend	Zurich	**KK Ray**	London	**T Turner**	Cincinnati
W Koenig	Munich	**RS Wright**	Rochester	**PLJ Wijngaard**	Parsippany
D Curcio	Parsippany	**MJ Jaros**	Chicago	**LA Leiter**	Toronto
JJP Kastelein	Amsterdam				

On behalf of the ORION-9 investigators

ORION-9: Acknowledgements

Contributions from 46 sites in 8 countries

Lead enrolling investigators

Canada	Jean Bergeron	Daniel Gaudet
Czech Republic	Victor Adamkova	Lucie Solcova
Denmark	Erik Schmidt	Ib Christian Clausen
Netherlands	Frank Visseren	Erik Stroes
South Africa	Elaine van Nieuwenhuizen Nyda Fourie	Iftikhar Ebrahim Soritza Coetzer
Spain	Jose Luis Diaz Diaz Xavier Pinto Sala	Daniel Zambon Rados
Sweden	Mats Eriksson	Stefano Romeo
United States	Traci Turner	John Homan

ORION-9: Background and rationale

HeFH highly prevalent and clinically challenging

A genetic disorder affecting 1 in 250 or ~30 million people worldwide[1]

- Life-long cumulative exposure to highly elevated LDL-C, starting at birth
- Drives early onset, accelerated atherosclerotic cardiovascular disease
- Over 90% not identified or properly diagnosed

LDL receptor gene mutations account for >90% cases[2]

- APOB (5%) and PCSK9 (<2%) mutations account for most other cases
- Monogenic mutation not identified in up to 30% of subjects with a clinical diagnosis[3]

Management is primary prevention of ASCVD through LDL-C lowering therapy[4,5,6]

- High intensity statins ± ezetimibe ± monoclonal antibodies against PCSK9

1. Nordestgaard et al. Eur Heart J 2013;34:3478-3490.
2. Berberich and Hegele. Nat Rev Cardiol 2019;16:9-20
3. Talmud et al. Lancet 2013381:1293-301
4. Defesche et al. Nature Reviews 2017;3:17093 doi:10.1038/nrdp.2017.93
5. Raal et al. Lancet 2015;385:331-340
6. Kastelein et al. J Clin Lipidol 2017;11:195-203

ORION-9: Background and rationale

Phase I-II studies identified twice-yearly dose potential

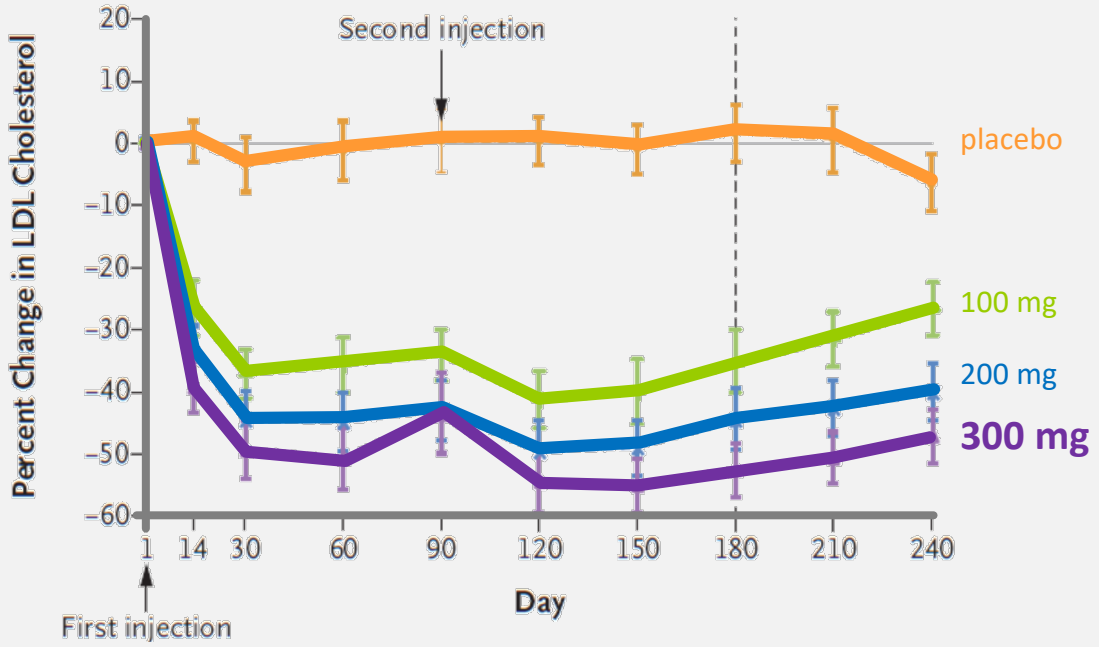
Inclisiran is a small interfering double-stranded RNA[1]

- Harnesses natural process of RNAi in liver

Dose-finding[2] and PD modeling[3] showed durable, potent effects on LDL-C

- 300 mg led to 53% lowering of LDL-C
- Extension studies affirmed long-term effect

Selected data from ORION-1 dose finding study



The NEW ENGLAND JOURNAL of MEDICINE

1. Fitzgerald et al. N Engl J Med. 2016;376:41-51
2. Ray et al. N Engl J Med 2017; 376: 1430-40
3. Kastelein personal communication at NLA Annual Meeting, Miami, May 2019

ORION-9: Objectives

Efficacy and safety over 18 months in subjects with HeFH

Study endpoints

1. Effectiveness

Co-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

Treatment response by FH genotype

ORION-9: Patient entry criteria

Heterozygous FH diagnosed by genotype or phenotype

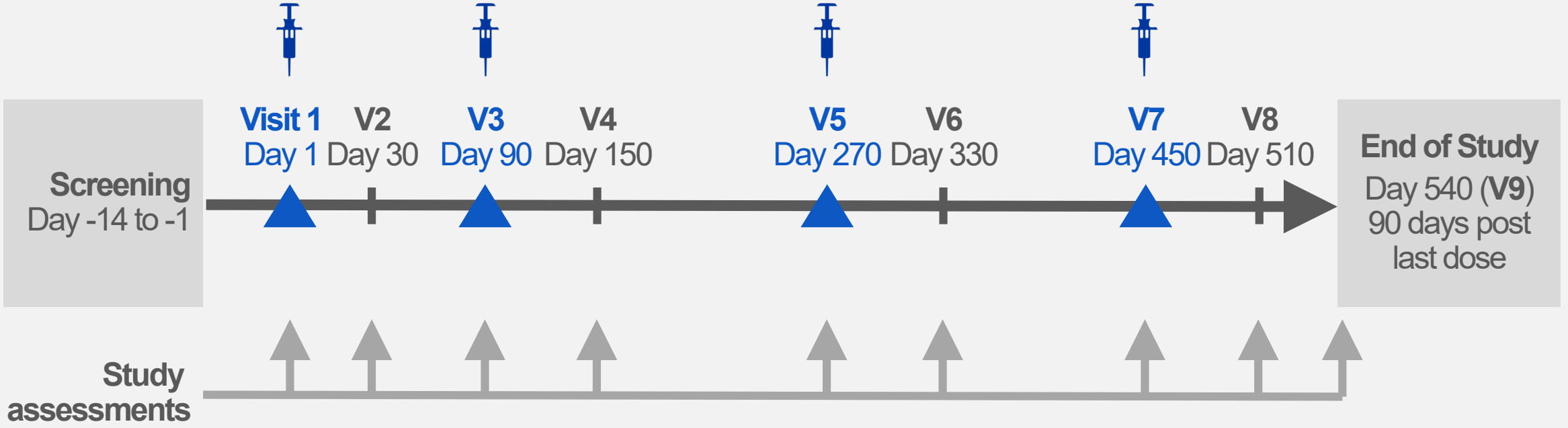
Inclusion criteria	Exclusion criteria
Age ≥18 years	Prior (90d) or planned use of PCSK9 mAbs
HeFH diagnosed by genetic testing and/or Simon Broome criteria[1]	MACE within 3 months of randomization
LDL-C ≥100 mg/dL (2.6 mmol/L)	NYHA class III-IV HF — or LVEF 30%
Stable on a low-fat diet	Uncontrolled severe hypertension
Maximally tolerated statin doses	Severe concomitant non CV disease
Ezetimibe allowed	Fasting TG >400 mg/mL (4.52 mmol/L)
Informed consent	Pregnant, nursing or without contraception

1. BMJ. 1991; 303: 893–896.

ORION-9: Study design

Eighteen months treatment and observation

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



ORION-9: Genotyping

Methods of genotyping met current standards

For subjects who consented to participate in the genetic sub-analysis

Next generation sequencing performed

- Coding regions of LDLR (exons 1-18), APOB (1-29), PCSK9 (1-12), LDLRAP1 (1-9)
- Pair-end DNA sequencing on the Illumina MiSeq sequencing platform
- 2º and 3º analysis with commercial bioinformatics software
- Variants aligned to GRCh37/hg19 reference genome; classified by current guidelines[1,2]

LDLR variants grouped

- Pathogenic
- Likely pathogenic
- Uncertain significance

1. Richards S, et al. Genet Med 2015;17(5):405-24.
2. Chora et al. Genet Med 2018;20:591-598. doi: 10.1038/gim.2017.151

ORION-9: Statistical plan

Sample size sufficient and alpha spending controlled

Sample size assumptions required 400 eligible patients

- Mean LDL-C reduction will be no less than 30 mg/dL (SD 20 mg/dL) with 5% drop outs
- >90% power to detect 30% lowering of LDL-C level with one-sided α = 0.025

Alpha spending controlled for co-primary and secondary efficacy endpoints

- Family-wise type I error rate controlled using a sequential testing procedure
- Hochberg procedure applied for secondary endpoints

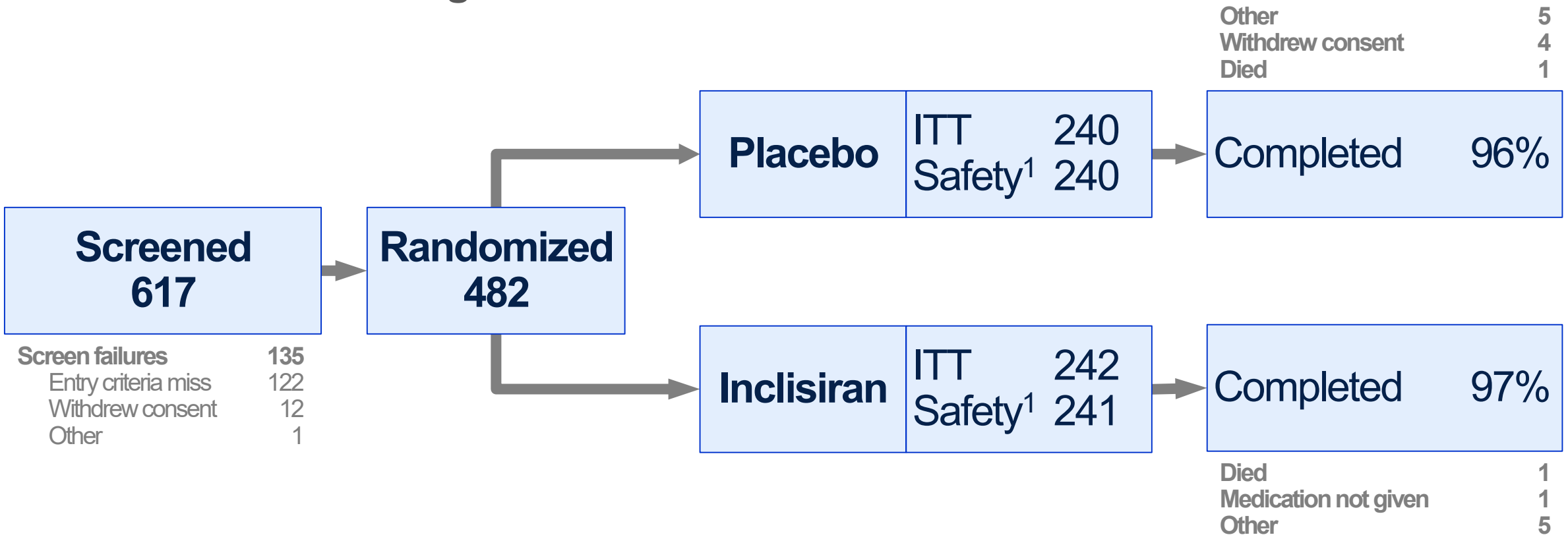
Pre-specified imputation methods used to account for missing data

Pre-specified sub-group analyses by FH genotype

ORION-9: Patient disposition

High proportion of patients completed 18 month study

Abbreviated consort diagram



1. Safety population comprises any subject given any study medication

ORION-9: Patients

High-risk phenotypes balanced by randomization

Patient characteristic ITT population[1]	Placebo N = 240	Inclisiran N = 242
Age median (IQR) – years	56 (47, 63)	56 (46, 64)
Female gender	125 (52%)	130 (54%)
Atherosclerotic cardiovascular disease	73 (30%)	59 (24%)
Lipid management treatment		
Statins	217 (90%)	219 (91%)
Of which high intensity statins given	171 (79%)	185 (84%)
Ezetimibe use	135 (56%)	120 (50%)
Baseline LDL-C mg/dL (±SD)[2]	**155 (58)**	**151 (50)**

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

ORION-9: Patients

Genotyping results for 432 patients giving consent

Genetic variants		Placebo		Inclisiran	
ITT population[1]		N = 240		N = 242	
Genetic testing performed		**211**		**221**	
LDLR variants		131	(55%)	125	(52%)
Of which	Pathogenic	118	(90%)	113	(90%)
	Likely pathogenic	9	(7%)	8	(6%)
	Uncertain significance	4	(3%)	4	(3%)
Two variants (‘double’)		15	(6%)	22	(9%)
APOB variants		11	(5%)	12	(5%)
PCSK9 gain of function variant		0		1	(0.4%)
No variant detected		54	(23%)	61	(25%)

1. All patients who were randomized, analyzed according to randomization

ORION-9

Efficacy results

ORION-9: Efficacy

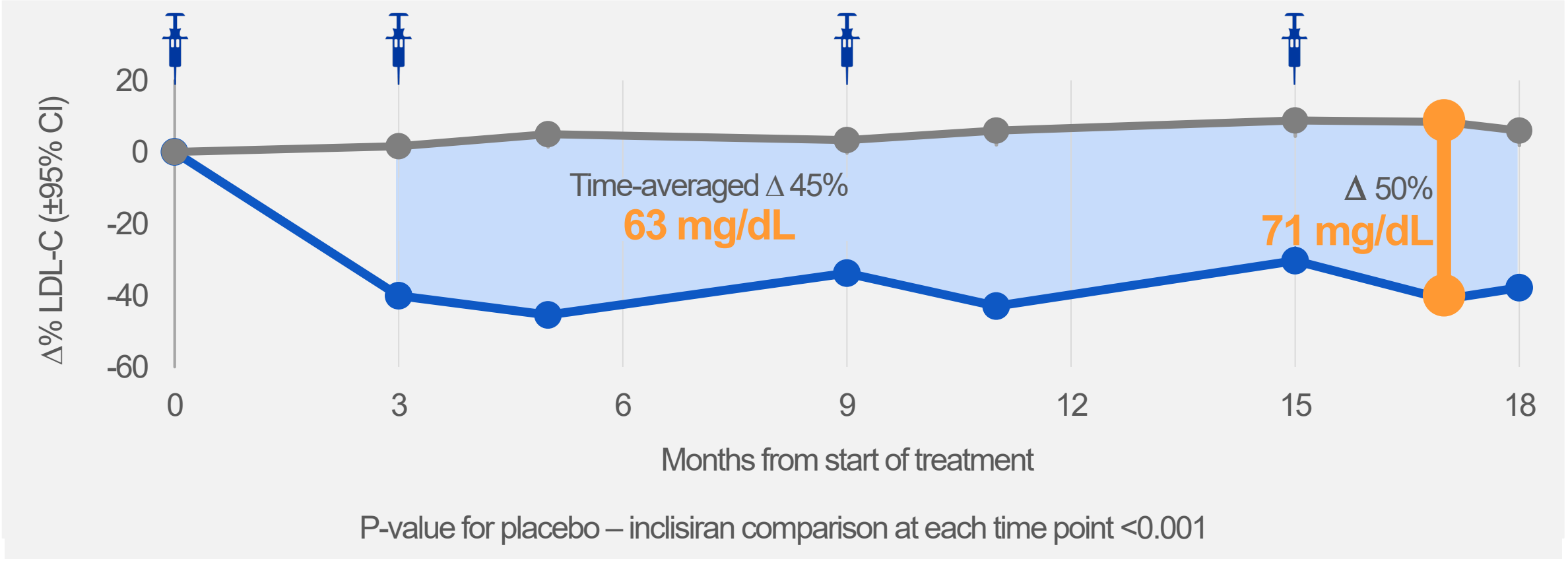
Highly significant lowering of LDL-C relative to placebo

Treatment group	N (ITT)	Percent change LDL-C			
		Mean at day 510		Time-averaged day 90 - 540	
		Observed	Imputed[1]	Observed	Imputed[2]
Placebo	240	+ 8	+ 8	+ 6	+ 6
Inclisiran	242	- 41	- 40	- 39	- 38
Difference (1º endpoint)		**- 50%**	**- 48%**	**- 45%**	**- 44%**
P-value		**<0.0001**		**<0.0001**	

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

ORION-9: Efficacy
Durable and potent effect over 18 months

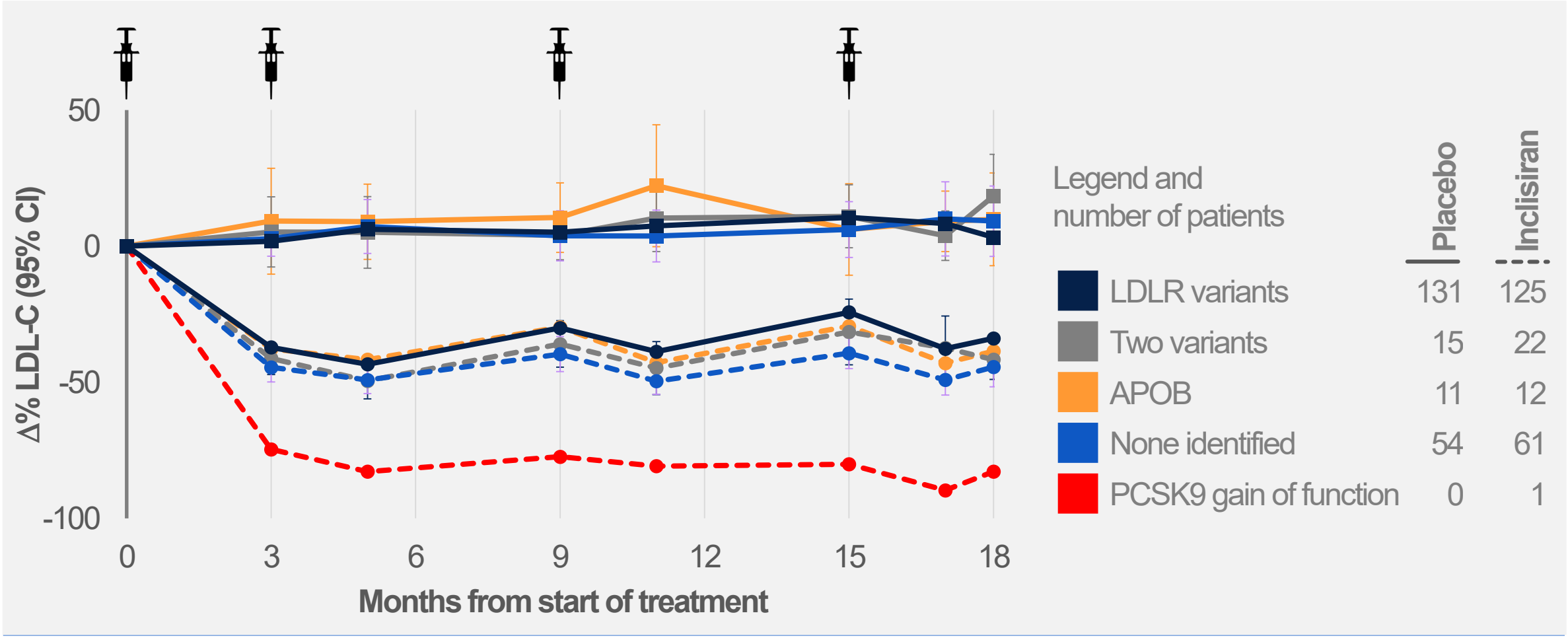
Percent and absolute change in LDL-C over time – observed values in ITT patients



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

ORION-9: Efficacy

Change in LDL-C by genetic variants



ORION-9

Safety results

ORION-9: Safety and tolerability

Safety profile similar to placebo

Treatment emergent adverse event (TEAE) Safety population[1] – AEs in ≥5% patients	Placebo N = 240	Inclisiran N = 241
Patients with at least one TEAE	172 (72%)	185 (77%)
Nasopharyngitis	20 (8%)	28 (12%)
Influenza	21 (9%)	13 (5%)
Upper respiratory tract infection	16 (7%)	16 (7%)
Back pain	10 (4%)	17 (7%)
Gastroenteritis	6 (3%)	11 (5%)

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-9: Safety and tolerability

AEs at injection site mostly mild and all transient

TEAEs at injection site Safety population[1]	Placebo N = 240		Inclisiran N = 241		Δ
Protocol-defined event	**1**	**(0.4%)**	**33**	**(13.7%)**	**13.3%**
(Reaction, erythema, rash, pruritus, hypersensitivity)					
Mild	1	(0.4%)	29	(12.0%)	11.6%
Moderate	0		4	(1.7%)	1.7%
Severe	0		0		
Persistent	0		0		

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

ORION-9: Safety and tolerability

No evidence of liver, kidney, muscle or platelet toxicity

Laboratory tests Safety population[1,2]		Placebo N = 240		Inclisiran N = 241	
Liver function	ALT >3x ULN	1	(0.4%)	3	(1.2%)
	AST >3x ULN	1	(0.4%)	2	(0.8%)
	ALP >2x ULN	0		2	(0.8%)
	Bilirubin >2x ULN[3]	3	(1.2%)	4	(1.7%)
Kidney function	Creatinine >2 mg/dL	1	(0.4%)	1	(0.4%)
Muscle	CK >5x ULN	5	(2.1%)	4	(1.7%)
Hematology	Platelet count <75x10^9/L	1	(0.4%)	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-9: Safety and tolerability

No difference in serious adverse events

Serious TEAEs Safety population[1,2]	Placebo N = 240		Inclisiran N = 241	
Patients with at least one serious TEAE	**33**	**(13.8%)**	**18**	**(7.5%)**
All cause death	1	(0.4%)	1	(0.4%)
Cardiovascular	0		1	(0.4%)
Cancer	0		0	
New, worsening or recurrent malignancy	3	(1.2%)	2	(0.8%)
Pre-specified exploratory CV endpoint[3]	**10**	**(4.2%)**	**10**	**(4.2%)**

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 CV basket of non-adjudicated terms cardiac death, and any signs or symptoms of cardiac arrest, non-fatal MI and/or stroke

ORION-9: Summary and conclusions

Inclisiran lowered LDL-C durably and safely in HeFH

Well-powered 18 month double-blind randomized placebo controlled HeFH trial

ORION-9 met all primary and secondary efficacy endpoints

- 71 mg/dL (50%) observed LDL-C lowering at day 510
- 63 mg/dL (45%) observed time-adjusted LDL-C lowering day 90-540
- On top of statins (>90%) and ezetimibe (>50%)
- Robust reduction in LDL-C with all underlying FH genotypes

Safety profile of inclisiran was similar to placebo in a high-risk population

- Adverse event incidence and laboratory values not different
- Injection site events were ~13% higher on inclisiran – mostly mild and all transient

Inclisiran shows potential to address the unmet need of high risk HeFH patients