European Society of Cardiology (ESC) Congress ORION-11 Investor Conference Call

Paris, September 2, 2019

Agenda

Welcome

- Krishna Gorti, Senior Vice President, Investor Relations

Overview

- Mark Timney, CEO

ORION-11 Results

- Kausik Ray, M.D., Principal Investigator of ORION-11, Professor of Public Health and Primary Care at Imperial College London

Q&A Session

Safe Harbor

Forward-looking statements

Statements contained in this presentation that are not purely historical, including, but not limited to, statements about the Company, the proposed offering described herein and the use of proceeds therefrom, are forward-looking statements for purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Without limiting the foregoing, the words “believes,” “anticipates,” “plans,” “expects,” “should,” “could,” “conviction”, and “potential,” and similar expressions, are intended to identify forward-looking statements. These forward-looking statements involve known and unknown risks and uncertainties that may cause the Company’s actual results, levels of activity, performance or achievements to be materially different from those expressed or implied by these forward-looking statements. Important factors that may cause or contribute to such differences include the ability of the Company to effectively develop inclisiran; whether inclisiran will advance in the clinical trials process on a timely basis or at all, or succeed in achieving its specified endpoints; whether the Company will make regulatory submissions for inclisiran on a timely basis; whether its regulatory submissions will receive approvals from regulatory agencies on a timely basis or at all; the extent of the commercial success of inclisiran, if approved; the strength, durability and life of the Company’s patent protection for inclisiran and whether the Company will be successful in extending exclusivity; and such other factors as are set forth in the risk factors detailed from time to time in the Company’s periodic reports and registration statements filed with the SEC, including, without limitation, the risk factors detailed in the Company's Quarterly Report on Form 10-Q filed with the SEC on July 24, 2019. The Company specifically disclaims any obligation to update these forward-looking statements.

2019 is a defining year for MDCO

We believe that inclisiran is a potential game-changer in treatment of CVD

- Almost 80% of high-risk patients do not reach guideline-recommend LDL-C targets
- Up to two-thirds of patients do not adhere to proven first-line cholesterol-lowering treatments after one year
- Inclisiran is the first cholesterol-lowering therapy in the siRNA class
- It is the only medicine in late-stage clinical development with the potential to assure durable and potent lowering of LDL cholesterol through twice-yearly dosing that gets patients to goal and keeps them there
- Today we presented strong ORION-11 data which bolsters our confidence in inclisiran's robust therapeutic profile
- Data strengthens our conviction that inclisiran addresses two critical unmet needs – additional LDL-C lowering and poor adherence – to get many more patients to goal

ORION-11

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

KK Ray London

D Kallend Zurich
RS Wright Rochester
JP Kastelein Amsterdam
LA Leiter Toronto
D Raal Johannesburg
W Koenig Munich
PL Wijngaard Parsippany

On behalf of the ORION-11 investigators

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

21-23^{mer} double strand small interfering RNA

Small-interfering double-stranded RNA

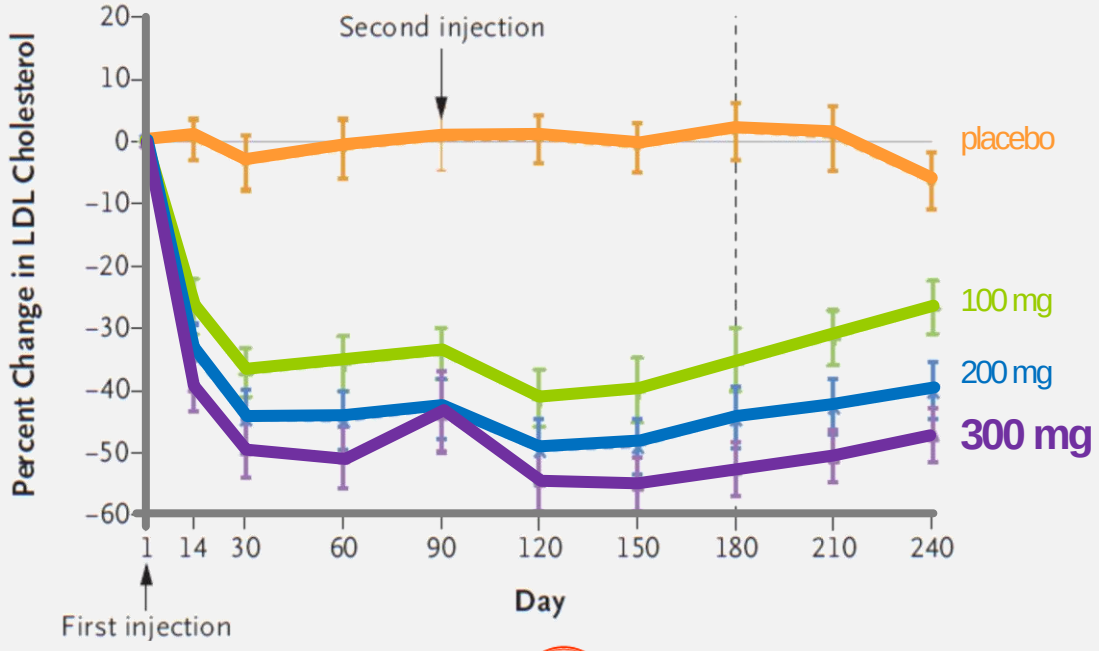
- Harnesses the natural process of RNAi
- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 specifically, durably and potently

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



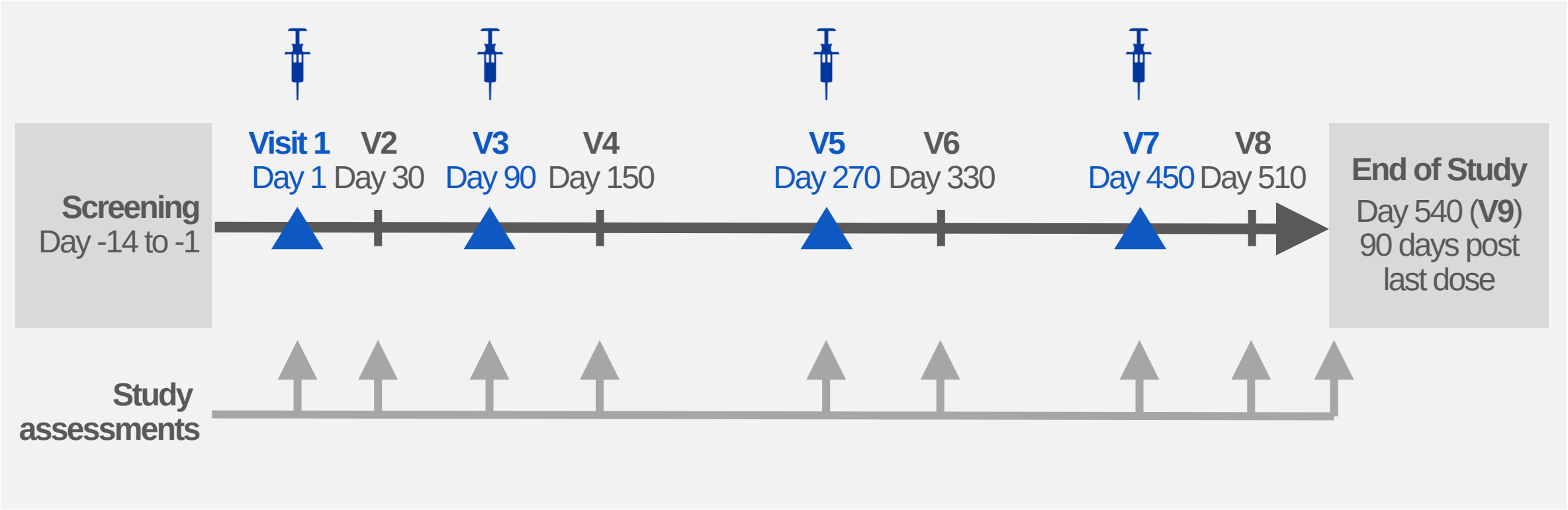
The NEW ENGLAND JOURNAL of MEDICINE

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

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

Age ≥18 years

ASCVD or risk equivalent patients[1]
- ASCVD LDL-C ≥70 mg/mL
- Risk equivalent LDL-C ≥100 mg/mL

Statin treatment
- Maximally tolerated doses
- Documented intolerance

Ezetimibe allowed

Informed consent required

Exclusion criteria

Prior or planned use of PCSK9 mAbs

MACE within 3 months of randomization

NYHA class III-IV HF — or LVEF 30%

Uncontrolled severe hypertension

Severe concomitant non CV disease

Prior/planned other investigational drug

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 $\alpha = 0.025$

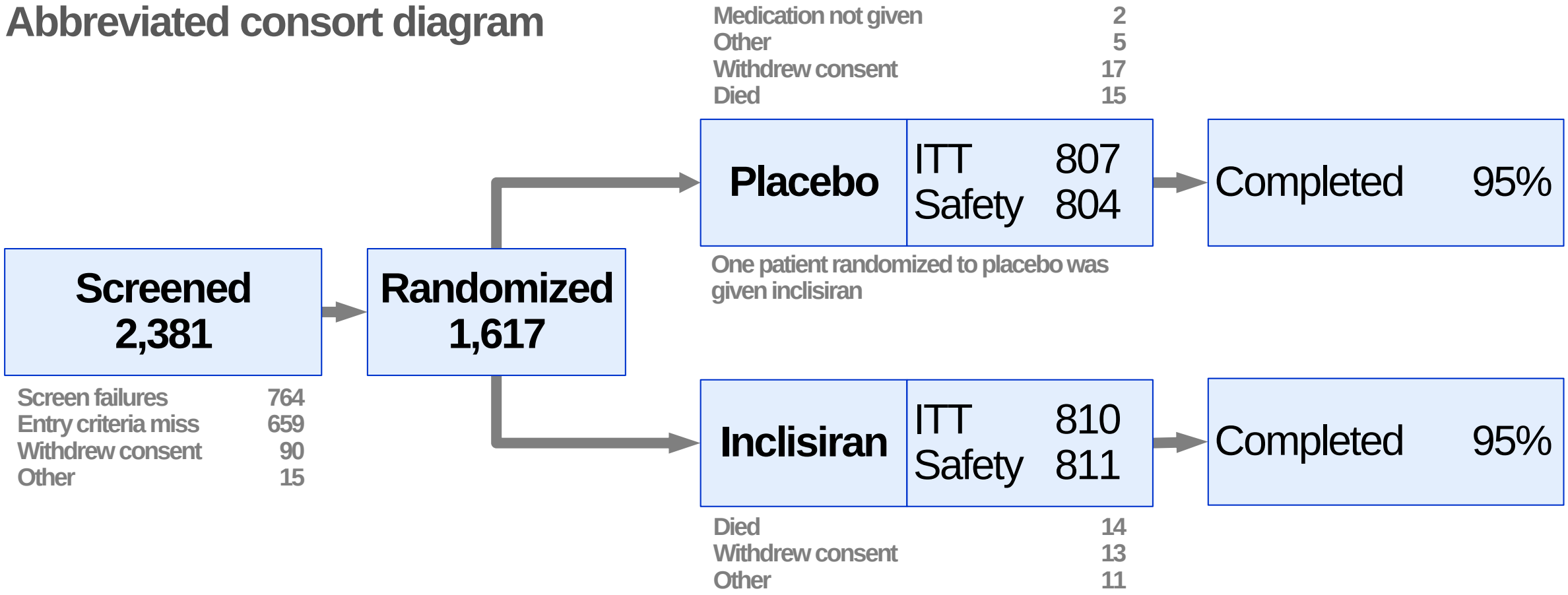
Primary endpoints
- Family-wise type I error rate controlled using a sequential testing procedure

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

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ORION-11
Efficacy Results

ORION-11: Efficacy

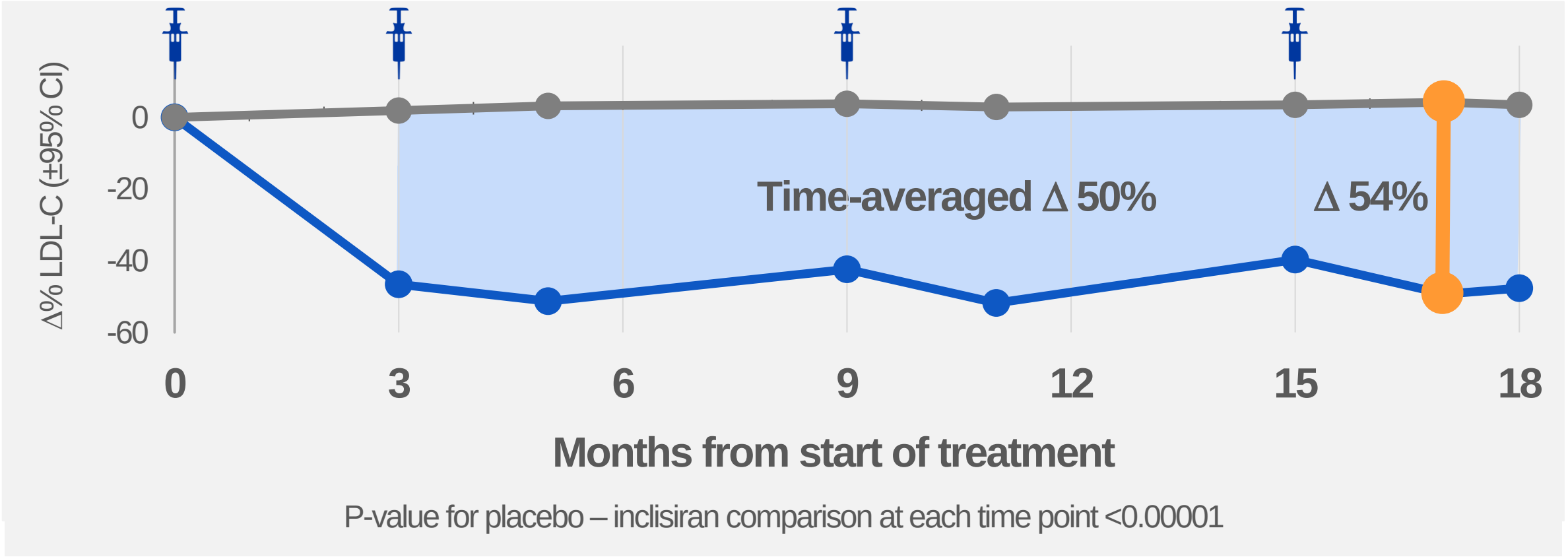
Highly significant lowering of LDL-C relative to placebo

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

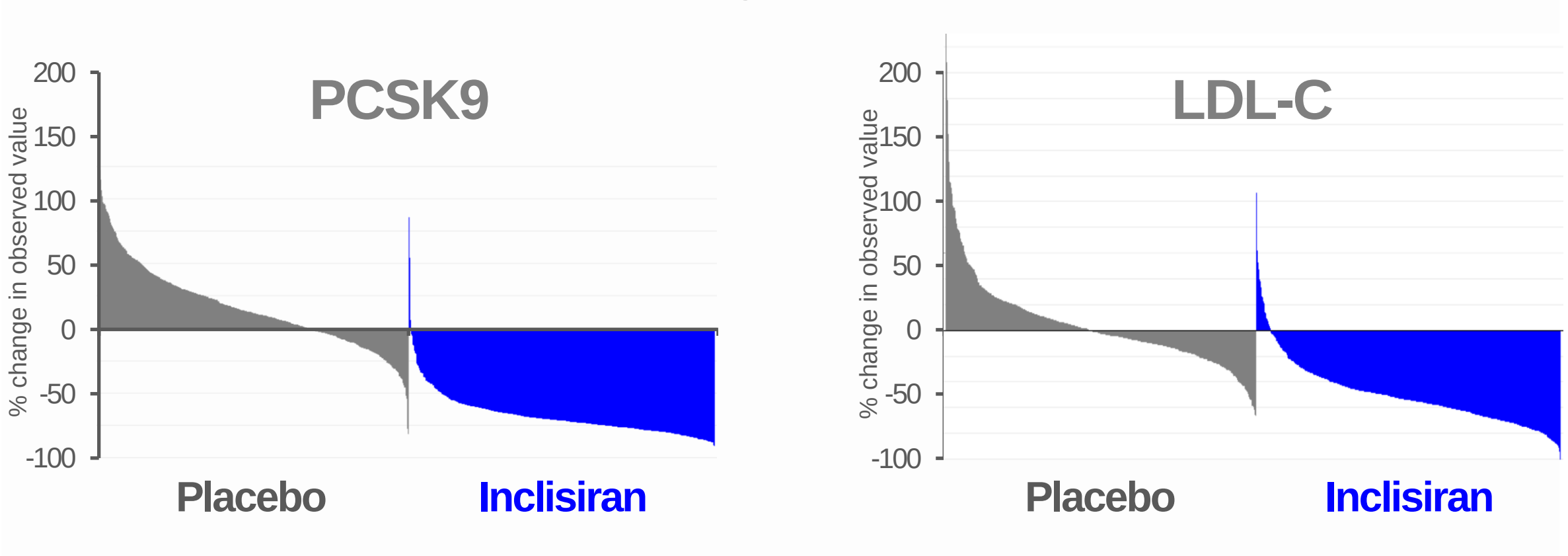


1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

ORION-11: Efficacy

Potent, consistent response to inclisiran

Individual patient responses contributing to primary endpoint -- 17 months



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ORION-11
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, predominantly 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
- Offers safe, convenient and assured results

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Q&A

Countdown to data
Anticipated news flow over next 6 months

Event	Timing
ORION-11 phase 3 data presentation at ESC Congress, Paris	September 2019 ✓
Expected sequential release of ORION-9 and -10 topline data	2H of 3Q 2019
Validation of manufacturing batches	3Q 2019
Submitted promissory abstracts to AHA for ORION-9 and -10	4Q 2019
Potential NDA submission	4Q 2019
Potential MAA submission	1Q 2020