ORION-9 & 10 Investor Conference Call

American Heart Association
Philadelphia • 18 Nov 2019

Safe Harbor

Forward-looking statements

Statements contained in this press release 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,” 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 October 30, 2019. The Company specifically disclaims any obligation to update these forward-looking statements.

Agenda

- **Welcome**
  - Krishna Gorti, Senior Vice President, Investor Relations
- **Overview**
  - Mark Timney, CEO
- **ORION-10 Results**
  - David Kallend, CMO
- **ORION-9 Results**
  - Professor Frederick Raal[1], University of Witwatersrand, Johannesburg
- **ORION Phase 3 Program – Summary Clinical Perspective**
  - John Kastelein[1], Emeritus Professor of Medicine, University of Amsterdam
- **Q&A Session**

1.Consultant to The Medicines Company

Reasons why we are here at AHA Scientific Sessions

Significant continued unmet needs in cardiovascular disease

1 in 3 deaths

in the U.S. is due to cardiovascular disease,[1] ahead of all other causes.[2,3]

Cumulative exposure to LDL-C

is understood to be causal to atherosclerotic cardiovascular disease (ASCVD), that can lead to events such as heart attack or stroke.[4]

1 in 4 heart attacks and strokes

are recurrent events.[1] Large studies consistently show that sustained, low-level LDL-C reduces ASCVD risk.[4]

~60 million people

with ASCVD or FH across U.S., largest European countries, China and Japan currently treated with LLT to manage CV risk.

>70% of patients

do not reach LDL-C thresholds of <70 mg/dL with statins and/or ezetimibe.[5,6]

Up to 2/3rds not adhering

to statins one year after starting treatment.[7]

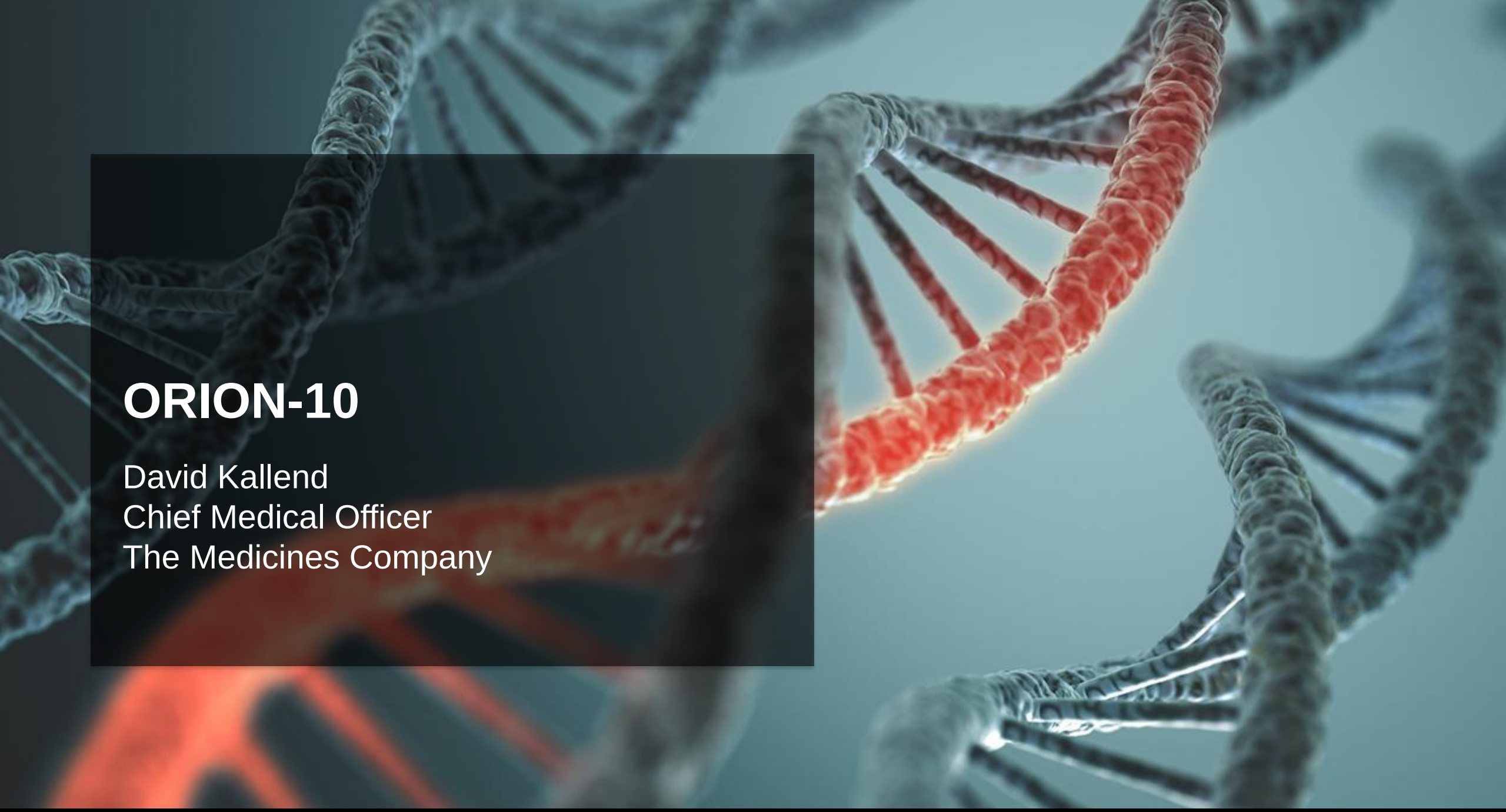
References

1. Benjamin EJ, et al. Circulation. 2019;139(10):e56-e528. **2.** McClellan M., et al. Circulation. 2019;139(9):e44-e54. **3.** CDC National Vital Statistics Reports (2018): Deaths: Leading Causes for 2016. **4.** Goldstein, Cell 2015; Skalen, Nature 2002; Tabas, Circ 2007; Nordestgaard, Eur Heart J 2013; Cuchel, Eur Heart J 2014. Ference, JACC 2018. **5.** Lansberg et al, Vasc Health Risk Manag. 2018;14:91-102. **6.** Cannon C, et al. JAMA Cardiol. 2017;2(9):959-966. **7.** Turin A, et al. J Cardiovasc Pharmacol Ther. 2015;20:447-56.

2019 is a defining year for MDCO

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

- **Inclisiran is the first and only cholesterol-lowering therapy in the siRNA class**
- **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**
- **This weekend we presented strong ORION-10 and -9 Phase 3 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-10

David Kallend
Chief Medical Officer
The Medicines Company

ORION-10: Background and rationale

Challenges remain in ASCVD patients

ASCVD remains the leading cause of death globally[1]

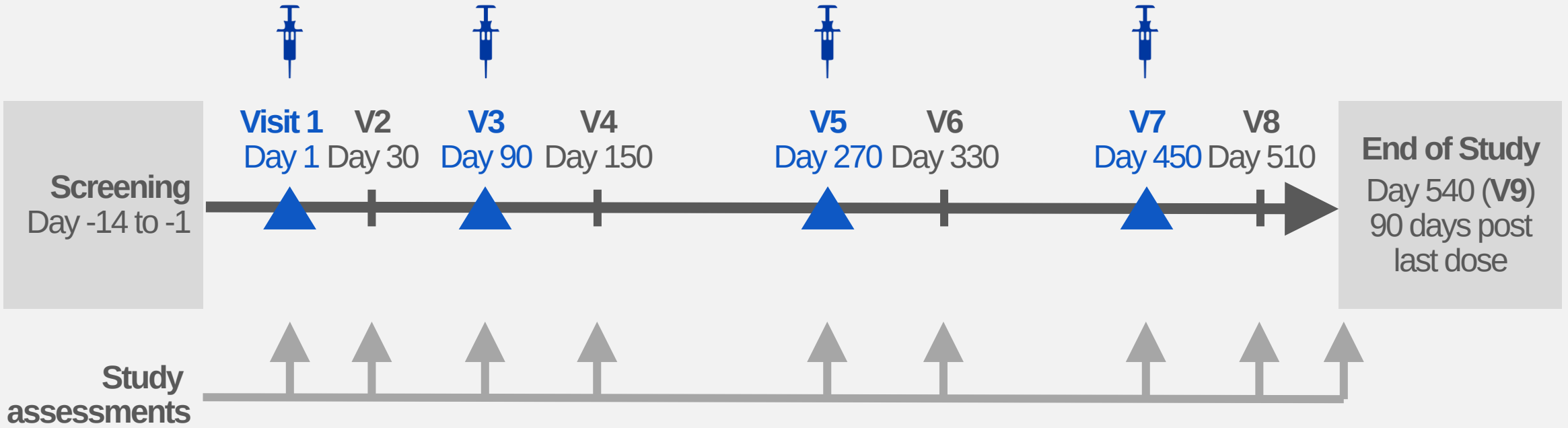
LDL-C lowering is the most effective intervention to change the course of ASCVD yet substantial residual risk remains despite aggressive treatment with statins and other agents.

- Lifestyle modification and statin treatment are foundational for secondary prevention[2,3]
- Ezetimibe and monoclonal antibodies to PCSK9 are adjunctive strategies to reduce LDL-C and clinical events by multiple treatment guidelines[4-6]

1. Benjamin et al. Circulation 2019;139:e56-e528.
2. Grundy et al. Circulation 2019;139:e1082-e143.
3. Mach F et al. European Heart Journal 2019 doi:10.1093/eurheartj/ehz455
4. Cannon et al. N Engl J Med 2015;372:2387-97.
5. Sabatine et al. N Engl J Med 2017;376:1713-22.
6. Schwartz et al. N Engl J Med 2018;379:2097-107

ORION-10: Study design
18 months treatment & observation in patients with ASCVD

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



ORION-10: Entry criteria

ASCVD patients not at LDL-C goal

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

ORION-10: 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

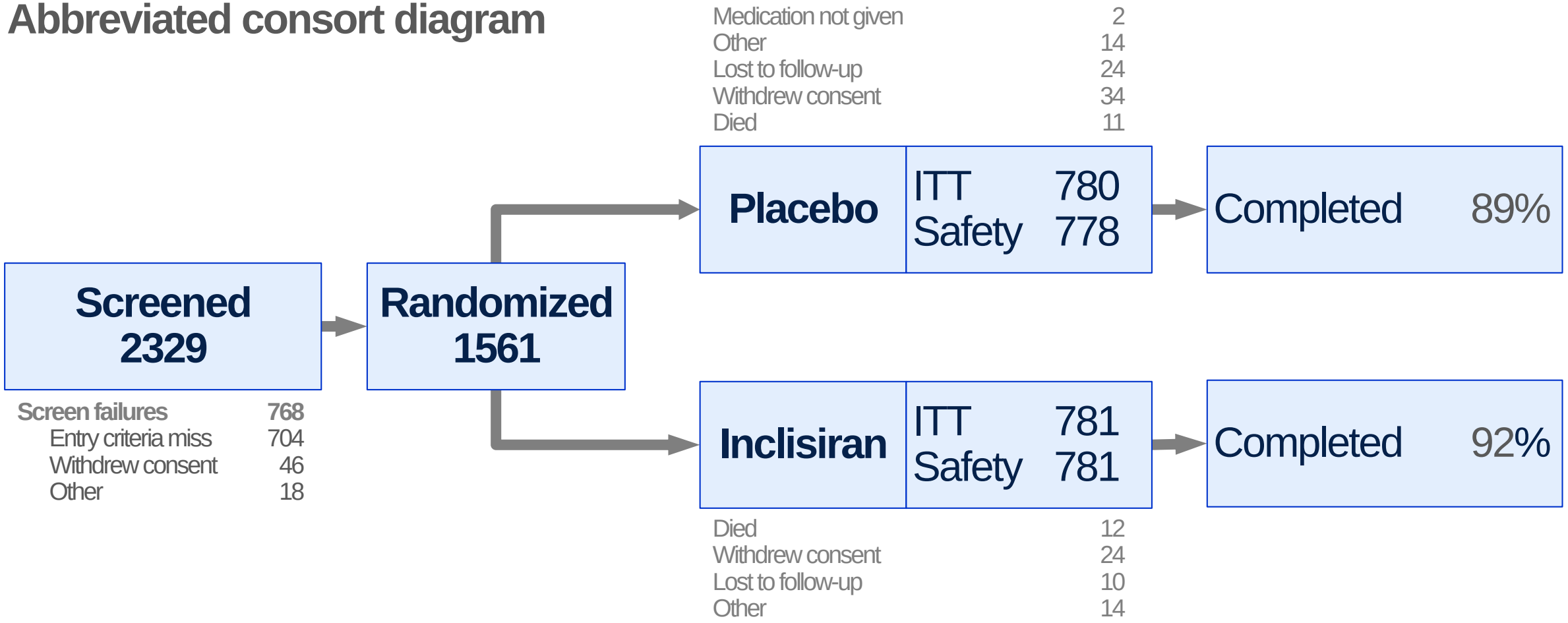
Cardiovascular events[1]

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

ORION-10: Patient disposition

High proportion of patients completed the study

Abbreviated consort diagram



Safety population comprises any subject given any study medication

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

ORION-10

Efficacy results

ORION-10: Efficacy

Highly significant lowering of LDL-C relative to placebo

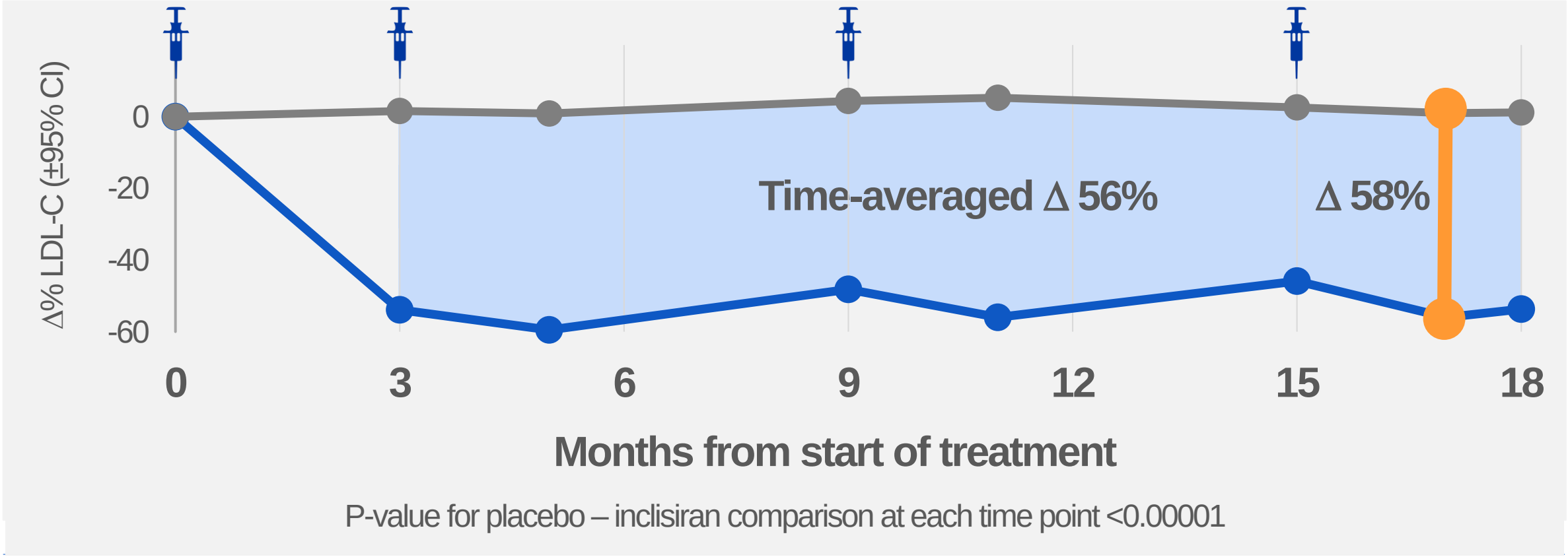
Treatment group	N (ITT)	Percent change LDL-C			
		Mean at day 510		Time-averaged day 90 - 540	
		Observed	Imputed[1]	Observed	Imputed[2]
Placebo	780	+ 1	+ 1	+ 3	+ 3
Inclisiran	781	- 56	- 51	- 53	- 51
Difference (1º endpoint)		**- 58**	**- 52**	**- 56**	**- 54**
P-value		**<0.00001**		**<0.00001**	

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

ORION-10: Efficacy

Durable and potent with consistent effect over 18 months

Percent 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-10

Safety results

ORION-10: Safety and tolerability

Adverse event profile similar to placebo

Treatment emergent adverse event (TEAE) Safety population[1] – AEs in ≥5% patients	Placebo N = 778		Inclisiran N = 781	
Patients with at least one TEAE	582	(75%)	574	(74%)
Diabetes mellitus adverse events	108	(14%)	120	(15%)
Hypertension	42	(5%)	42	(5%)
Back pain	39	(5%)	39	(5%)
Bronchitis	30	(4%)	46	(6%)
Upper respiratory tract infection	38	(5%)	37	(5%)
Dyspnea	33	(4%)	39	(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-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

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

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

ORION-10: Exploratory endpoint

Adverse cardiovascular events

Cardiovascular TEAEs Safety population[1,2]	Placebo N = 778		Inclisiran N = 781	
Pre-specified exploratory CV endpoint[3]	**79**	**(10.2%)**	**58**	**(7.4%)**
Cardiovascular death	5	(0.6%)	7	(0.9%)
Fatal or non-fatal MI or stroke[4]	26	(3.3%)	32	(4.1%)

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. MedDRA-defined CV basket of non-adjudicated terms cardiac death, and any signs or symptoms of cardiac arrest, non-fatal MI and/or stroke 4. Post hoc analysis

ORION-10: Summary

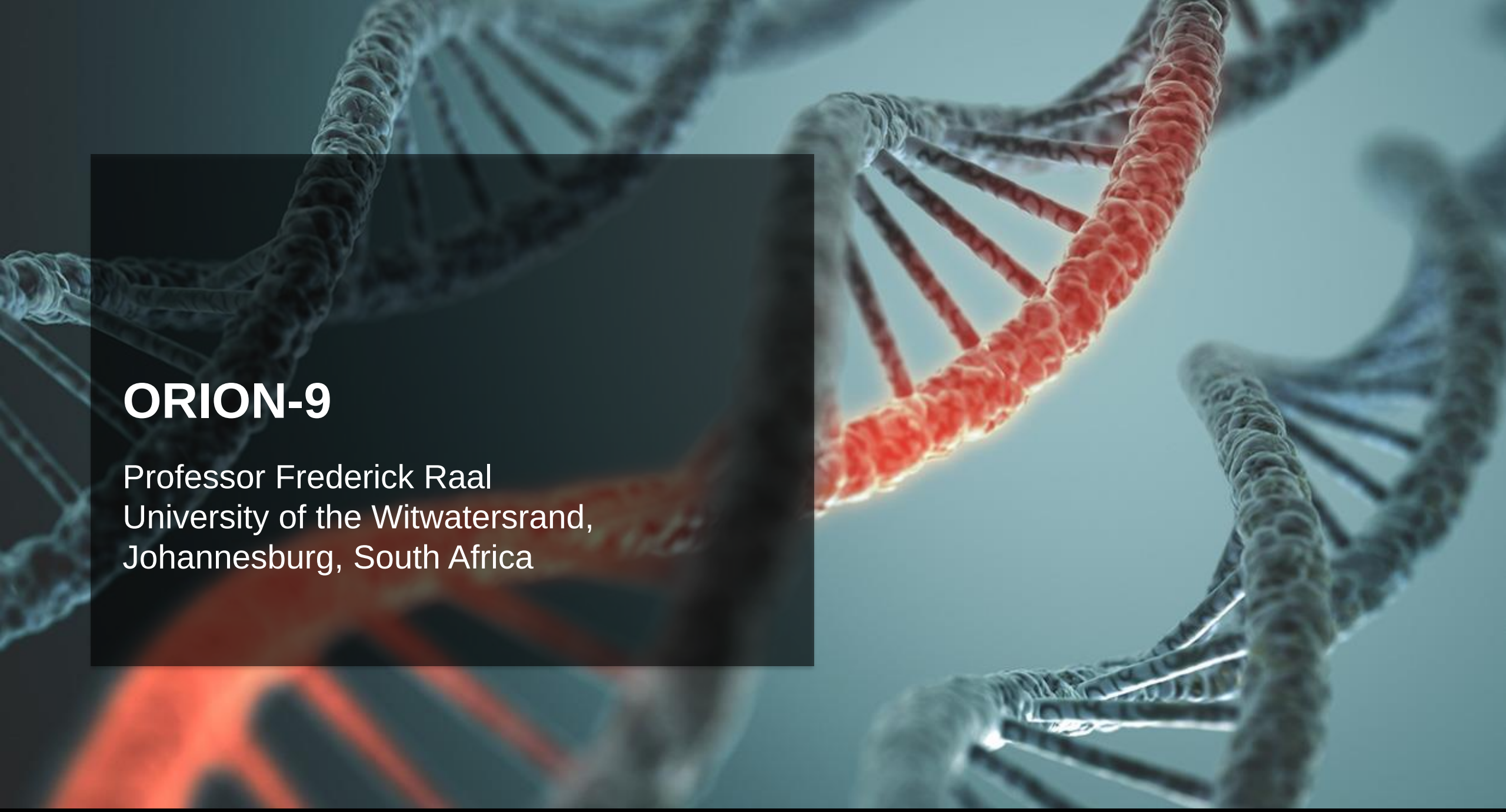
Twice-a-year inclisiran lowered LDL-C by ≥50% safely

Efficacy

- ORION-10 met all primary and secondary endpoints
- Inclisiran reduced the primary LDL-C endpoint
  - At 17 months by 58% (observed values) and 52% (imputed)
  - From month 3 to 18 by 56% (observed) and 54% (imputed)

Safety and tolerability

- Inclisiran safety profile was similar to placebo
- No adverse changes in laboratory markers
- Injection site events on inclisiran 2.6% - predominantly mild and none persistent
  - Numerically lower with prefilled syringe than with vial and syringe
- Exploratory basket of CV events numerically less frequent on inclisiran than placebo



ORION-9

Professor Frederick Raal
University of the Witwatersrand,
Johannesburg, South Africa

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: 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

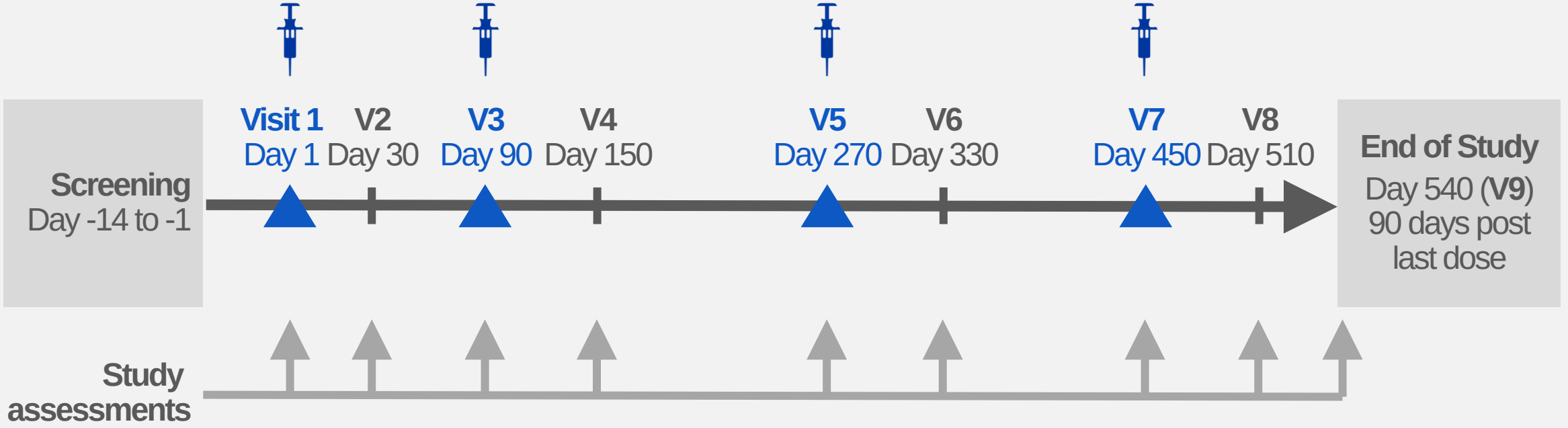
Inclusion criteria	Exclusion criteria
Age ≥18 years	Prior (90d) or planned use of PCSK9 mAbs
HeFH diagnosed by genetic testing and/or Simon Broome criteria[1]	MACE within 3 months of randomization
LDL-C ≥100 mg/dL (2.6 mmol/L)	NYHA class III-IV HF — or LVEF 30%
Stable on a low-fat diet	Uncontrolled severe 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

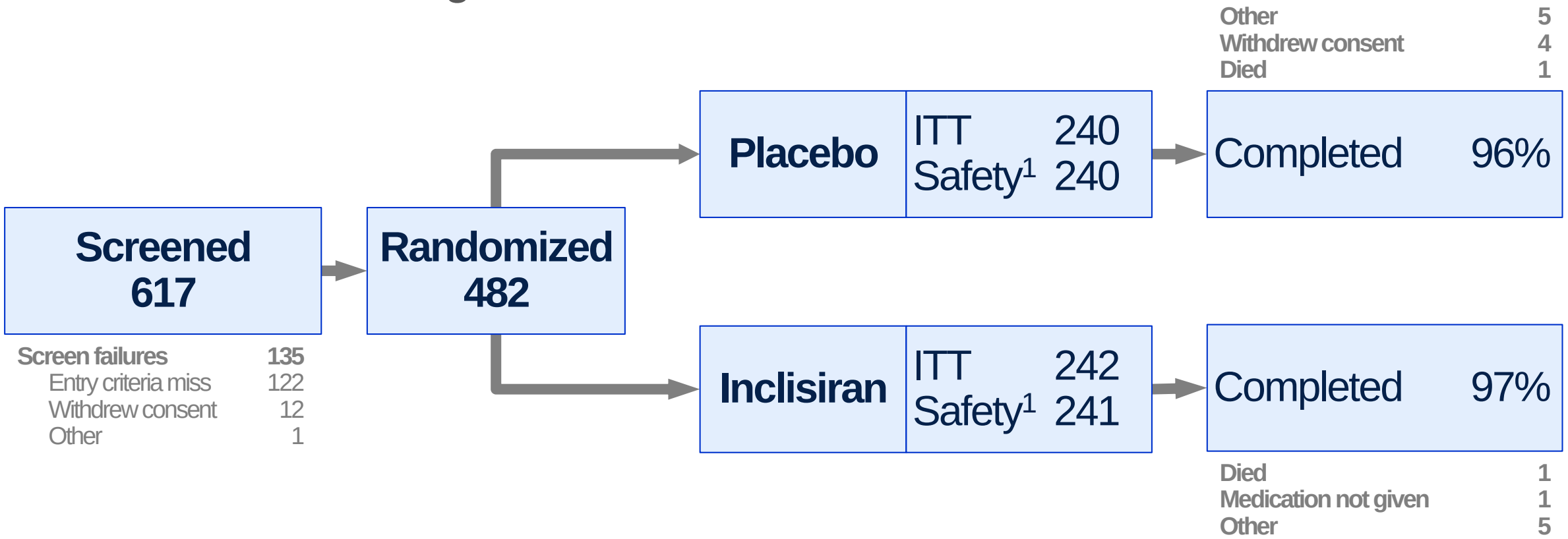
Randomized 1:1 inclisiran 300 mg *vs.* placebo – with maximally tolerated statins



ORION-9: 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	Placebo	Inclisiran
ITT population[1]	N = 240	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

Efficacy results

ORION-9: Efficacy

Highly significant lowering of LDL-C relative to placebo

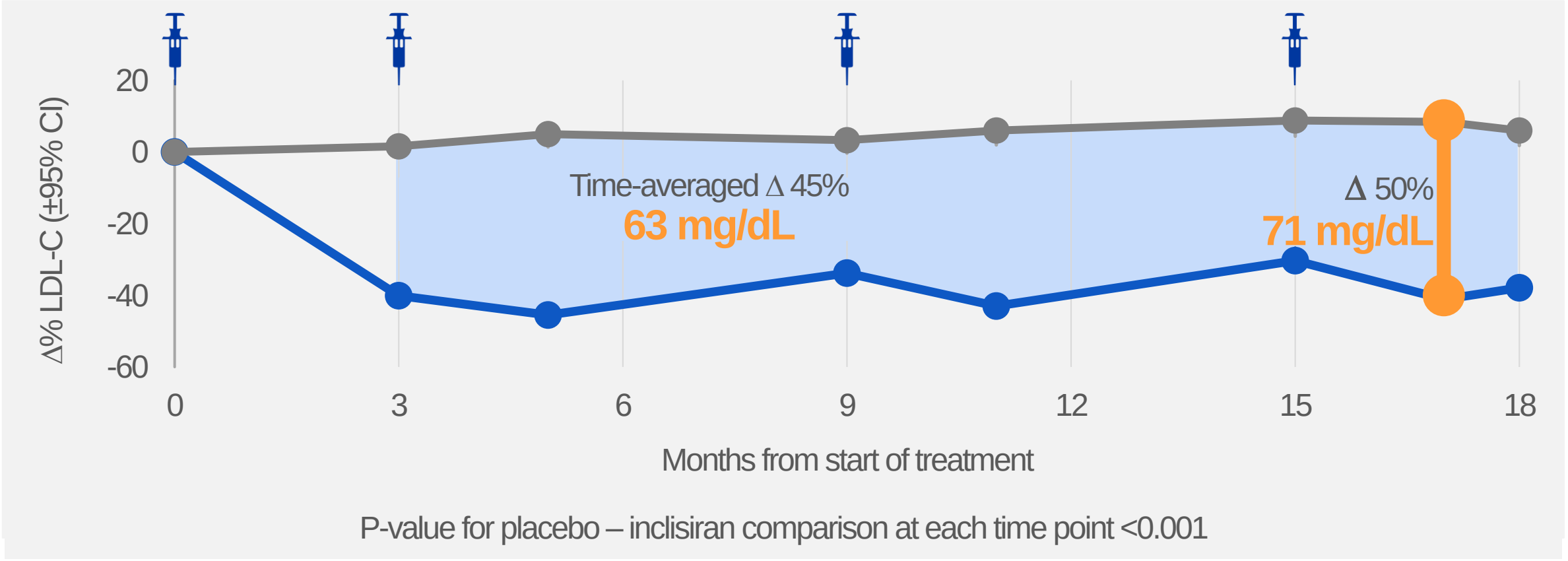
Treatment group	N (ITT)	Percent change LDL-C			
		Mean at day 510		Time-averaged day 90 - 540	
		Observed	Imputed[1]	Observed	Imputed[2]
Placebo	240	+ 8	+ 8	+ 6	+ 6
Inclisiran	242	- 41	- 40	- 39	- 38
Difference (1º endpoint)		**- 50%**	**- 48%**	**- 45%**	**- 44%**
P-value		**<0.0001**		**<0.0001**	

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

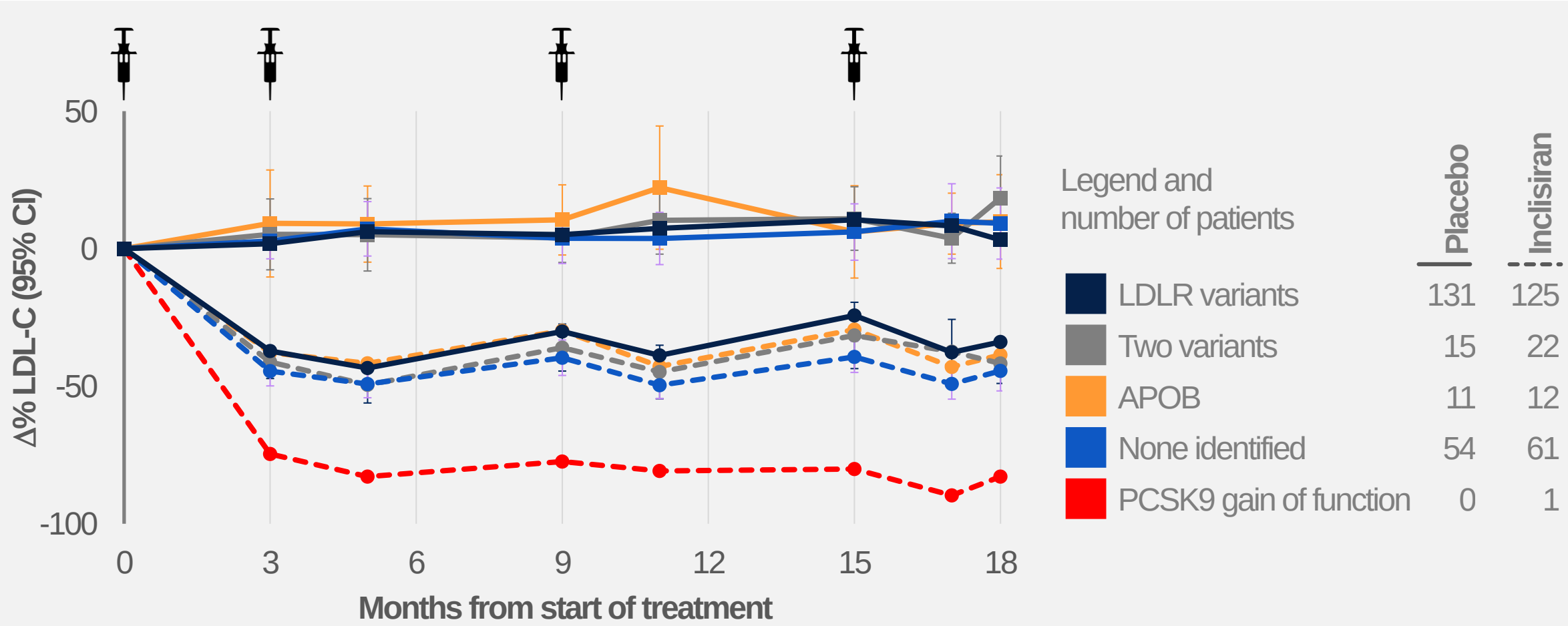
Percent and absolute change in LDL-C over time – observed values in ITT patients



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

ORION Phase 3 Program - Clinical Perspective

John Kastelein, M.D., Ph.D.
Emeritus Professor of Medicine
University of Amsterdam

ORION-10

Scott Wright et al.
AHA 2019

ASCVD

N =1,561 (ITT)
LDL-C = 105 mg/dL

ORION-11

Kosh Ray et al.
ESC 2019

ASCVD
Risk equivalents (13%)

N =1,617 (ITT)
LDL-C = 106 mg/dL

ORION-10+11

Combined data

ASCVD
Risk equivalents (6%)

N = 3,178 (ITT)
LDL-C = 105 mg/dL

ORION-10 & 11

Safety results

ORION-10+11 pooled data: Safety and tolerability of inclisiran

Injection site AEs infrequent, mostly mild and transient

Injection site TEAEs	Placebo		Inclisiran		Difference
Safety population[1]	N = 1,582		N = 1,592		
Protocol-defined event	**11**	**(0.70%)**	**58**	**(3.64%)**	**2.95%**
(Skin reaction, erythema, rash, pruritus, hypersensitivity)					
Mild	10	(0.63%)	36	(2.26%)	1.63%
Moderate	1	(0.06%)	22	(1.38%)	1.32%
Severe	0	( )	0	( )	
Persistent	0	( )	0	( )	

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

ORION-10+11 pooled data: Safety and tolerability of inclisiran

No evidence of liver, kidney, muscle or platelet toxicity

Laboratory tests Safety population[1]		Placebo N = 1,582		Inclisiran N = 1,592	
Liver function	ALT >3x ULN	6	(0.38%)	6	(0.38%)
	AST >3x ULN	9	(0.57%)	6	(0.38%)
	ALP >2x ULN	5	(0.32%)	6	(0.38%)
	Bilirubin >2x ULN[2]	11	(0.70%)	10	(0.63%)
Kidney function	Creatinine >2 mg/dL	41	(2.59%)	35	(2.20%)
Muscle	CK >5x ULN	17	(1.07%)	20	(1.26%)
Hematology	Platelet count <75x10^9/L	1	(0.06%)	1	(0.06%)

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

ORION-10+11 pooled data: Safety and tolerability of inclisiran

No difference in serious adverse events

Serious treatment emergent adverse events Safety population[1,2]	Placebo N = 1,582		Inclisiran N = 1,592	
Patients with at least one serious TEAE	**386**	**(24.4%)**	**356**	**(22.4%)**
All cause death	26	(1.6%)	26	(1.6%)
Cardiovascular	15	(1.0%)	16	(1.0%)
Cancer	6	(0.4%)	4	(0.3%)
New, worsening or recurrent malignancy	46	(2.9%)	42	(2.6%)

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

ORION-10+11 pooled data: Exploratory endpoint

Adverse cardiovascular events

Cardiovascular TEAEs Safety population[1,2]	Placebo N = 1,582	Inclisiran N = 1,592	Risk ratio	95% CI
Pre-specified exploratory cardiovascular endpoint[3]	**162 (10.2%)**	**121 (7.6%)**	**0.74**	**0.59 - 0.93**
Fatal and nonfatal MI & stroke[4]	56 (3.5%)	44 (2.8%)	0.78	0.53 – 1.15

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 non-adjudicated endpoints similar to those being used in ORION-4 e.g. MI, acute MI, ischemic stroke, CVA, cerebral infarct, hemorrhagic stroke.

ORION-10 & 11

Efficacy results

ORION-10+11 pooled data: Efficacy

Potent, durable, consistent lowering of LDL-C

Treatment group	N (ITT) 3,178	Mean observed percent change in LDL-C at day 510
Placebo	1,587	**+ 3**
Inclisiran	1,591	**- 53**
Difference (1º endpoint)		**- 56**
P-value		<0.00001

ORION-10+11 pooled data: Efficacy

Getting high-risk patients to AHA-recommended goals

Among 1,591 patients randomized to inclisiran

<70 mg/dL LDL-C threshold

>90%

≥50% LDL-C lowering

87%

1. Pre-specified endpoint: Percentage of patient reaching LDL-C level at any post-baseline visit
2. Pre-specified endpoint: Percent of patients reaching LDL-C level ≥50% reduction from baseline at any visit

Potential implications

What could this mean for the ORION-4 outcomes trial?

Using phase II – III data to predict CV outcomes

	Phase I-II data model	ORION 10-11	ORION 4
Baseline LDL-C (mg/dL)	**112**	**105**	**≥100 est.**
LDL-C lowering effects	**Predicted**	**Observed**	**15,000 patients 5 year follow-up**
1º endpoint: day 510 % LDL-C reduction	54%	56%	
Time-averaged % LDL-C reduction	51%	54%	
LDL-C reduction (mg/dL)	57 – 60	53 – 57	
Computed 5 year MACE RRR[1,2]	**0.67 – 0.69**	**0.68 – 0.69**	**~0.70 est.**

1. MACE relative risk reduction estimate assumes 50% of effect year-1; 100% of effect thereafter
2. Based on Cholesterol Treatment Trialists' (CTT) Collaboration (Baigent at al, 2005)

Potential implications

Which patients need more LDL-C lowering?

Highest risk hypercholesterolemia population not at goal

(Millions of patients)

	US[1]	EU5[2]	Japan[3]	China[4]	Total
FH or ASCVD	29.1	19.7	10.3	54.4	113.5
Treated with oral LLTs	22.0	12.2	4.7	20.4	59.3
Failing to reach LDL-C goal	**15.6** (71%)	**9.5** (79%)	**2.4** (51%)	**13.7** (67%)	**41.2** (70%)

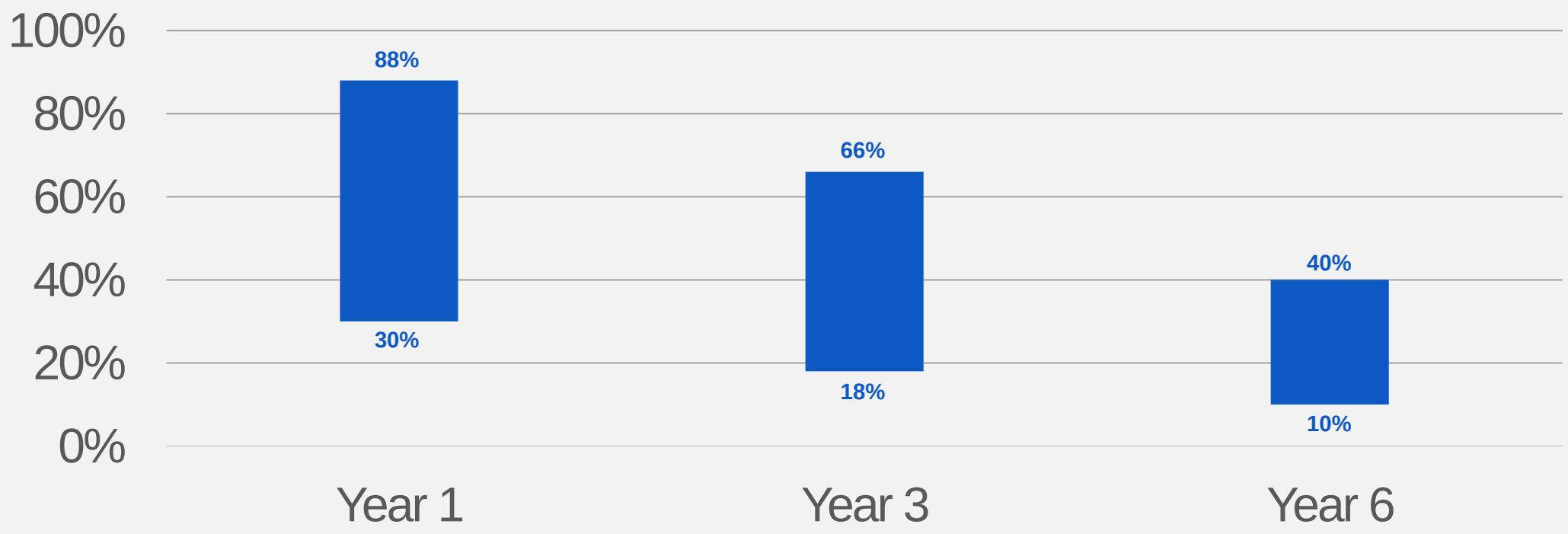
1. IQVIA LAAD 2018 data
2. ESC CVD statistics 2017; Steel et al. BMI 2017;7(2):e013255; Marz et al. atherosclerosis 2018;268:99-107; Geller et al. EHJ 2007;28:3051-58; Ferrieres et al. poster in ESC 2015; Khunti K, Danese MD, Kutikova L, et al. *JAMA Netw Open*. 2018;1(8):e185554; Sierra et al. Adv Ther 2015;32:944-961; Arca A et al. Atherosclerosis 2018;271:120-127. Teramoto T et al. Atherosclerosis 2016;24:8e254;
3. Nagar, et al. 2017; Circ J doi:10.1253/circj.CJ-17-0811
4. Danese et al. NHANES database, Ann Int Med 2013, Saurabh P. Nagar et al 2018, expert interviews

Potential implications

Taking on the intractable problem of poor adherence

Adherence in 22 statin data sets

Range of values reported



Mann et al, 2010

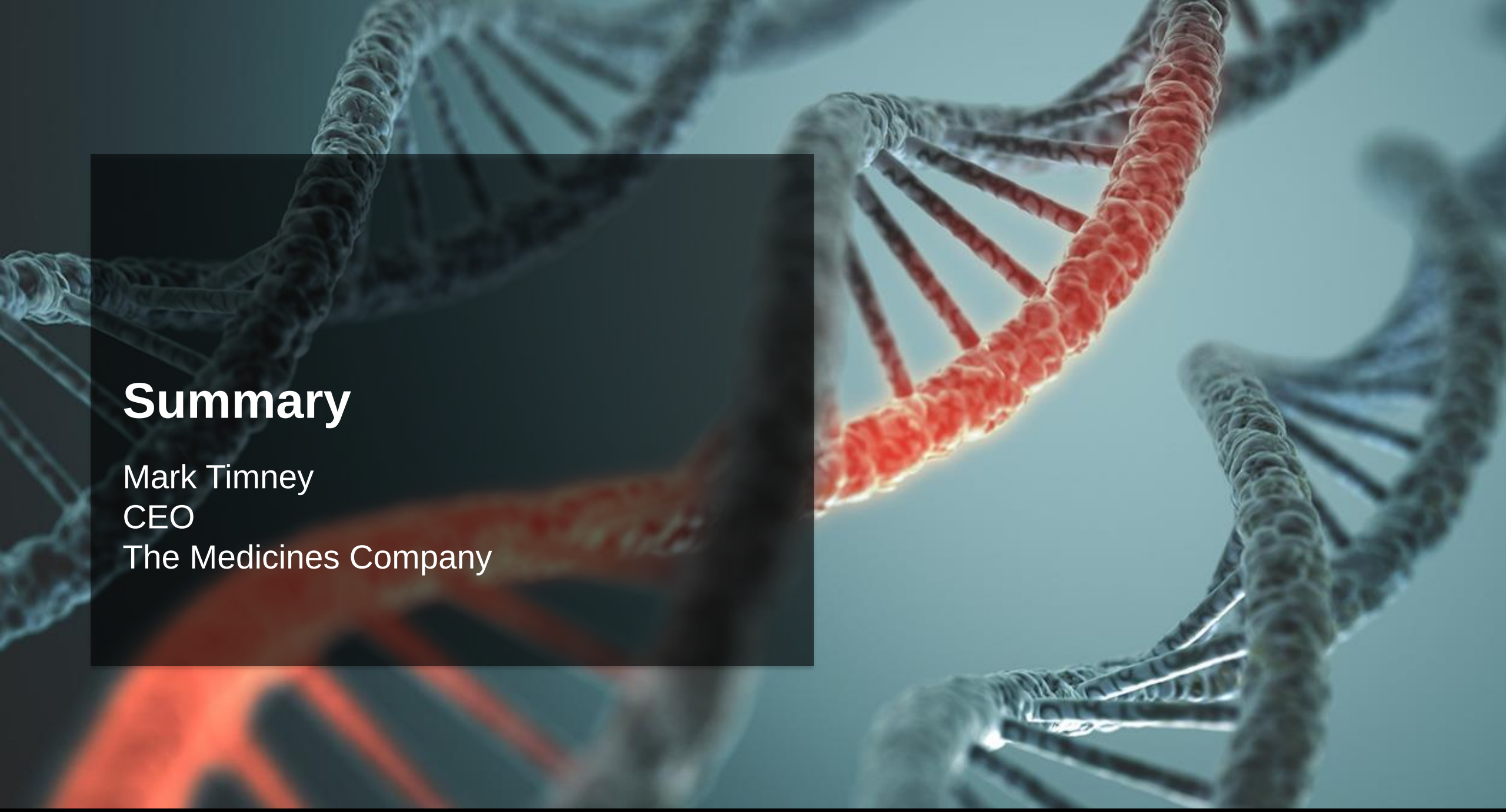
Potential implications

The opportunity of patient contact

Ninety percent US ASCVD patients visit an HCP at least twice a year

Place of visits	ASCVD with diabetes	ASCVD without diabetes
Clinic or health center	11%	11%
Doctor's office | HMO	85%	85%
Other (e.g. OPD)	4%	4%
Number of visits		
None	3%	4%
2 or more	**92%**	**88%**

Source: 1. Zhang S et al, AMCP, April 2018



Summary

Mark Timney
CEO
The Medicines Company

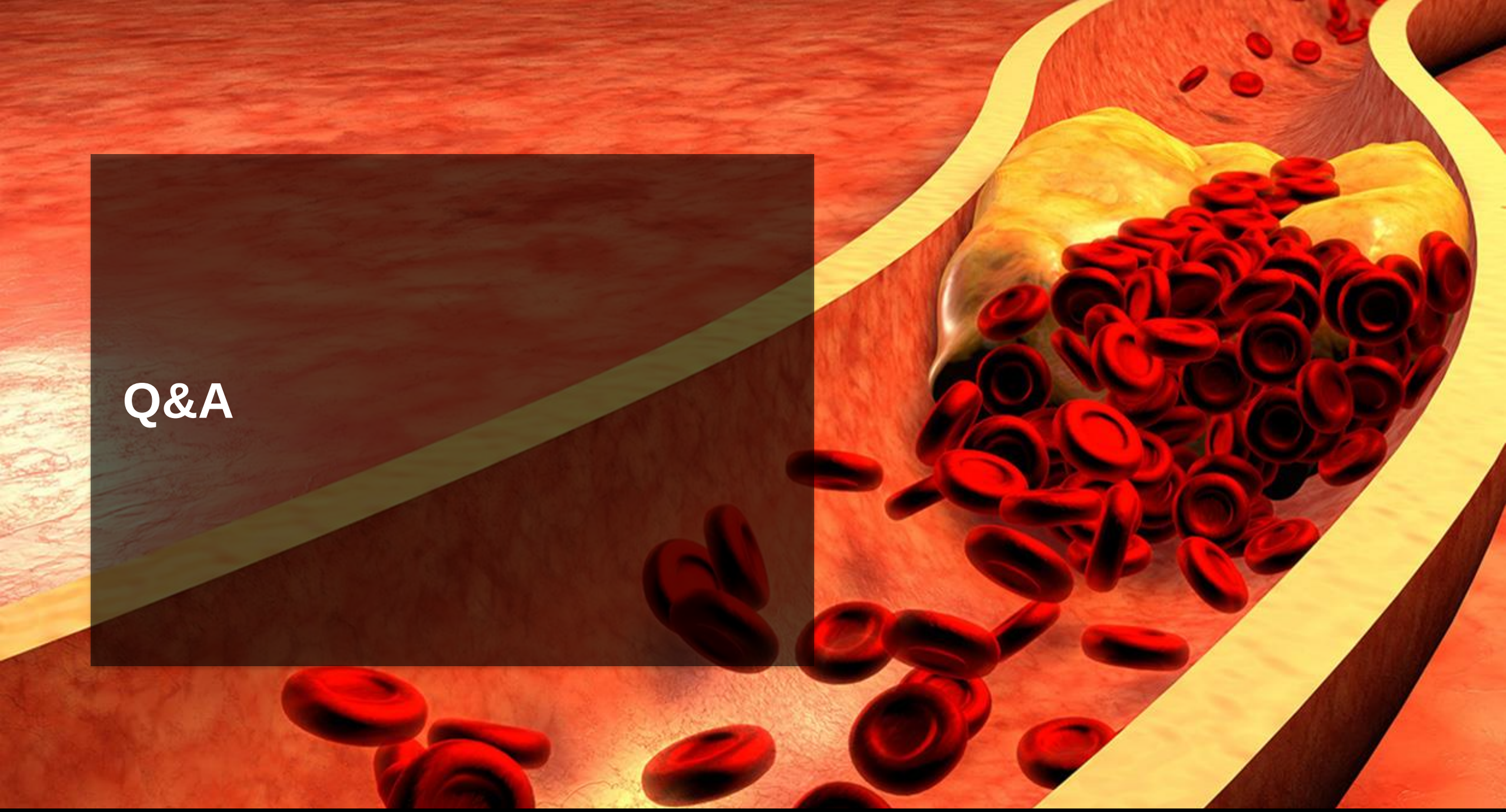
Conclusions and implications

Inclisiran is a potential game-changer in treatment of CVD

- **Inclisiran achieved durable and potent LDL-C reductions across Phase 3 program**
  - Unique co-primary endpoints demonstrate cumulative impact on LDL-C
  - Highly specific siRNA mechanism enables cumulative lowering of LDL-C
  - Twice-yearly dosing ideally suited to address cumulative exposure to LDL-C

- **Excellent safety profile in high-risk CVD populations**
  - Overall AE profiles similar between the placebo & inclisiran-treated groups
  - No treatment-related hepatic or renal abnormalities

- **Inclisiran potentially offers fundamentally different approach to current options**
  - Administration by HCP coincides with typical six-monthly patient visits
  - Helps clinicians get LDL low and keep it there over sustained period
  - Consideration of patient preference and improved adherence


Q&A

ORION-9 & 10 Investor Conference Call

American Heart Association
Philadelphia • 18 Nov 2019