ORION-10

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

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On behalf of the ORION-10 investigators

ORION-10: Background and rationale

Challenges remain in ASCVD patients

ASCVD remains the leading cause of death globally[1]

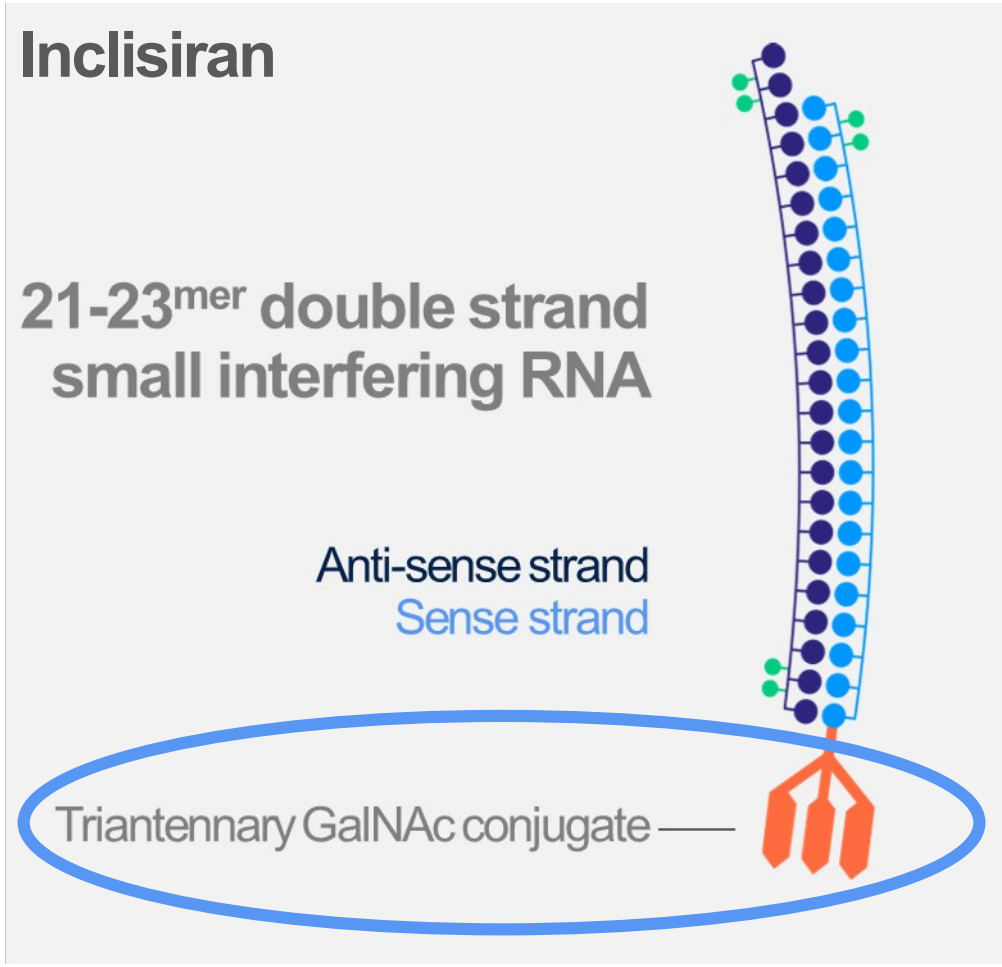
LDL-C lowering is the most effective intervention to change the course of ASCVD yet substantial residual risk remains despite aggressive treatment with statins and other agents.

- 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: Background and rationale

Harnessing the natural process of RNAi



Small interfering double-stranded RNA[1]

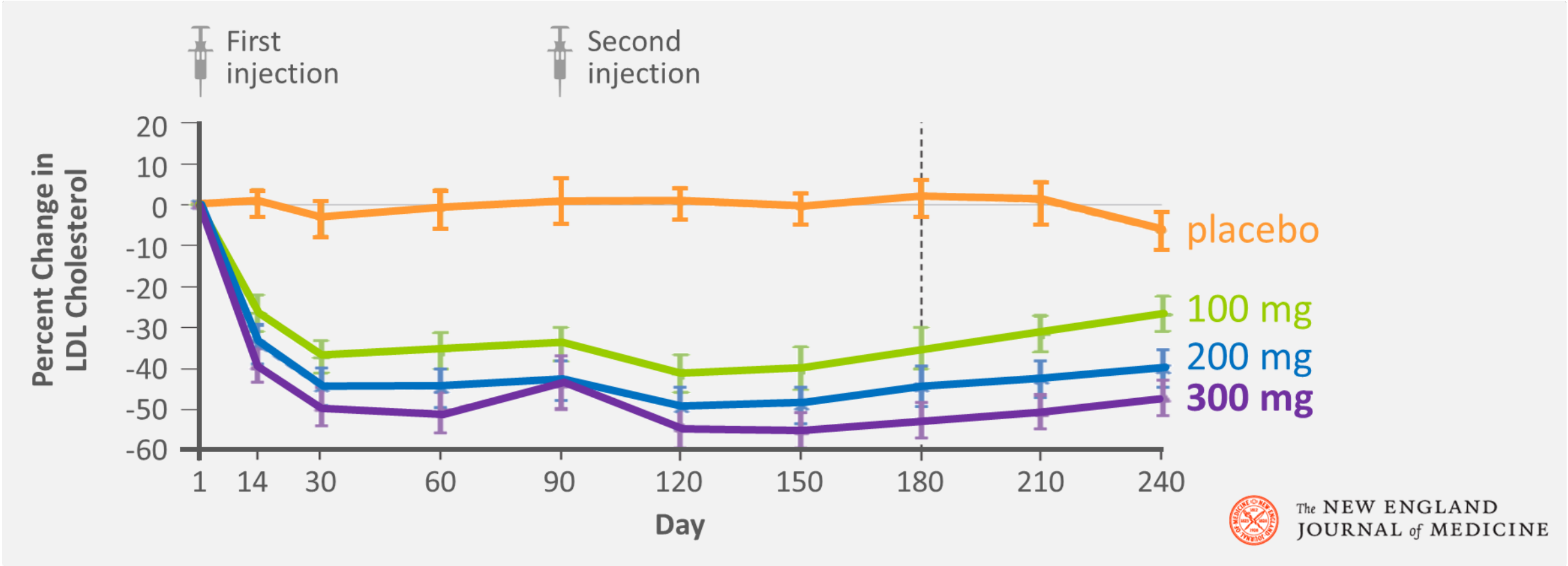
- Harnesses the natural process of RNAi
- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 in hepatocytes

Fitzgerald et al. N Engl J Med. 2016;376:41-51.

ORION-10: Background and rationale

Phase I-II studies identified twice yearly dose potential

Selected data from ORION-1 dose finding study[1]



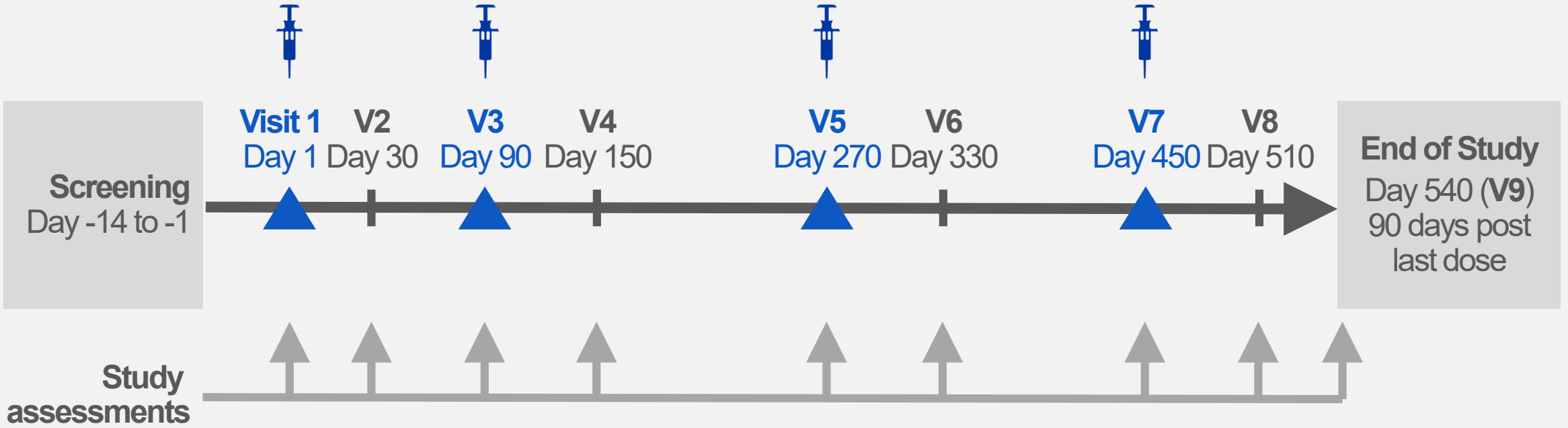
1. Ray et al. N Engl J Med 2017; 376: 1430-40

ORION-10
Purpose

To assess efficacy and safety of inclisiran 300 mg compared to placebo in a high risk population of ASCVD subjects using an 18 month placebo controlled trial.

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: 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 outs
- >90% power to detect 30% lowering of LDL-C level with one-sided α = 0.025

Primary endpoints

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

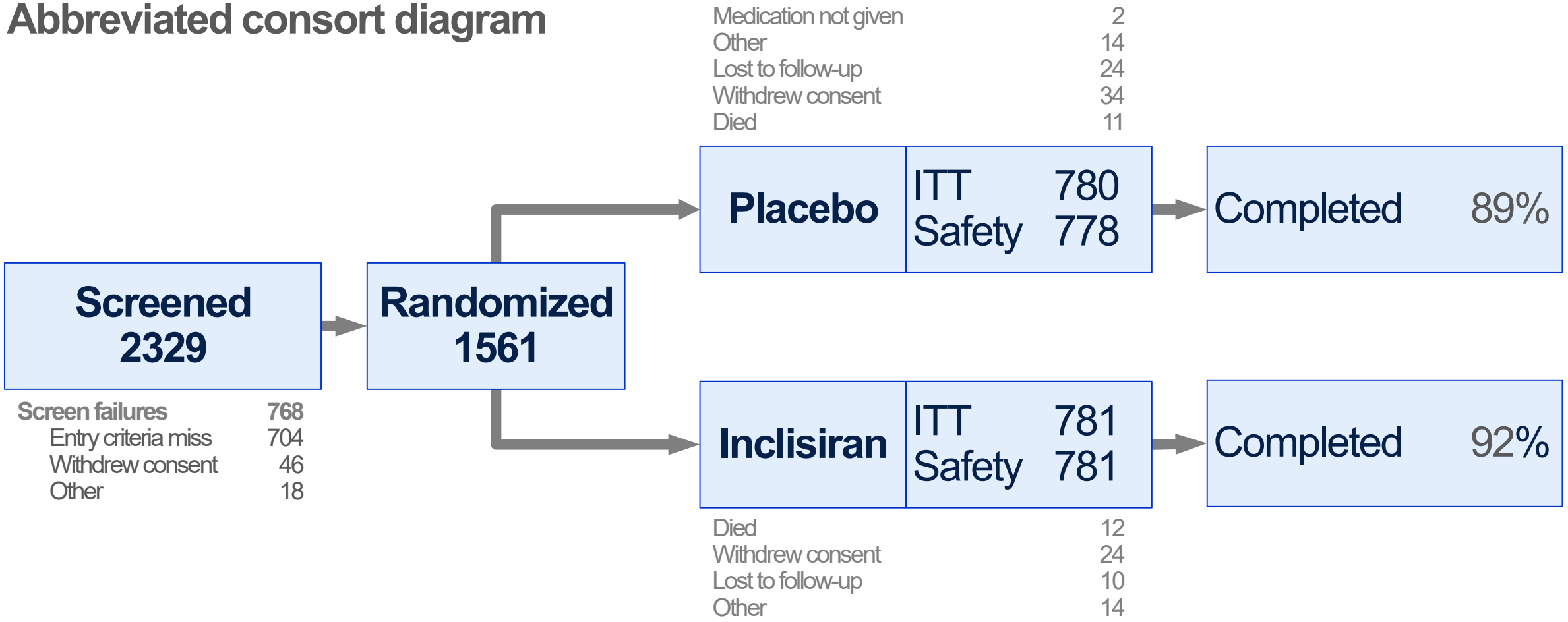
Sensitivity analysis for primary efficacy endpoints

- Pre-specified imputation and analysis methods used to account for missing data

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

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

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	780	+ 1	+ 1
Inclisiran	781	- 56	- 51
Difference (1º endpoint)		**- 58**	**- 52**
P-value			**<0.00001**

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

ORION-10: Efficacy

Highly significant lowering of LDL-C relative to placebo

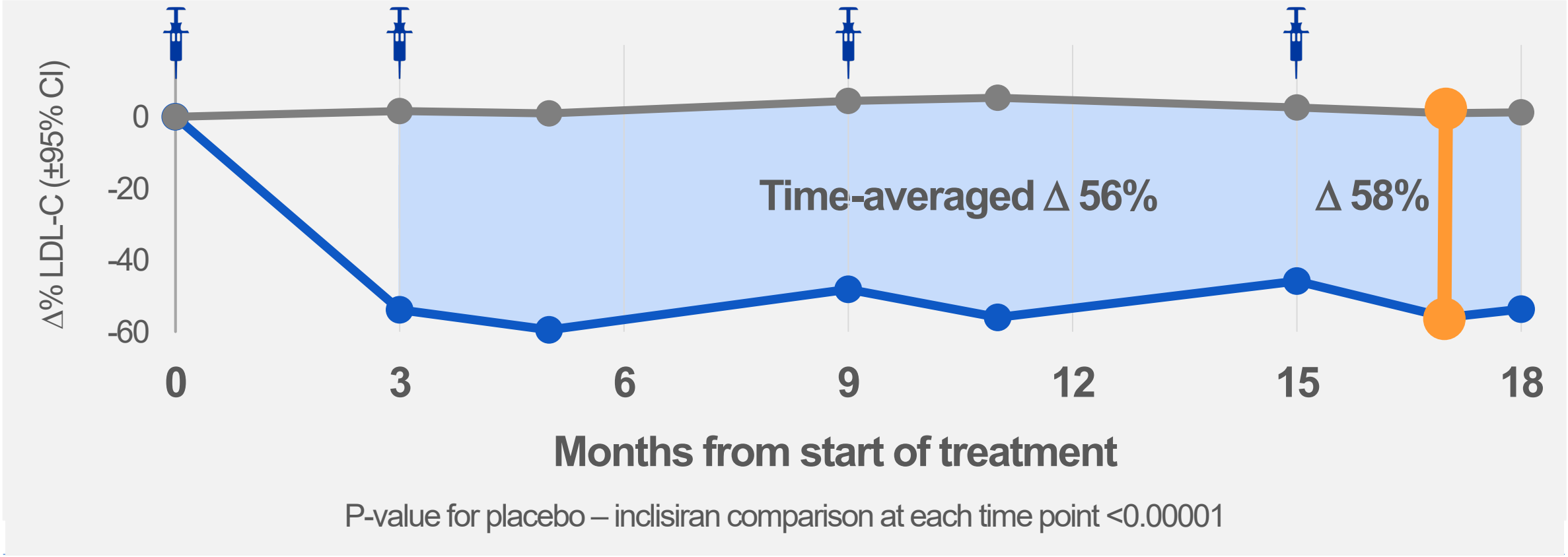
Treatment group	N (ITT)	Percent change LDL-C			
		Mean at day 510		Time-averaged day 90 - 540	
		Observed	Imputed[1]	Observed	Imputed[2]
Placebo	780	+ 1	+ 1	+ 3	+ 3
Inclisiran	781	- 56	- 51	- 53	- 51
Difference (1º endpoint)		**- 58**	**- 52**	**- 56**	**- 54**
P-value		**<0.00001**		**<0.00001**	

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-10: Conclusions and implications

Inclisiran is the first and only cholesterol lowering siRNA

Inclisiran achieved durable and potent LDL-C reduction with twice yearly injection in ASCVD patients on appropriate lipid lowering therapies over 18 months of follow-up with a safety profile similar to placebo in a high risk cardiovascular population

Assuming FDA approval, twice yearly administration coincides with typical twice yearly patient visits with HCP's

Inclisiran therefore potentially offers a novel new treatment for LDL-C

- Pre-filled syringe convenient and well tolerated
- Meaningful new choice for patients
- HCP opportunities for influencing medication adherence in routine clinical practice
- Safe, potent and durable LDL-C lowering results

ORION-10: Acknowledgements
Contributions from 145 sites in the United States

Lead enrolling investigators

Aslam Ahmad	Northwest Houston Clinical Research	**John Evans**	East Coast Institute for Research
Ferris George	East Coast Institute for Research	**John LeDoux**	CB Flock Research
Matthew Teltser	A&R Research Group	**David Ramstad**	Hampton Roads Center for Clinical Research
Neil Fraser	Troy Internal Medicine	**Jose Cardona**	Indago Research and Health
Alan Miller	Alta Pharmaceutical Research Center	**Andrew Waxler**	Northridge Hospital Medical Center
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Thank you