ORION

A pooled analysis of Phase III studies of inclisiran

RS Wright Rochester

D Kallend	Zurich	**LA Leiter**	Toronto	**CA Meanwell**	Parsippany
KK Ray	London	**U Landmesser**	Berlin	**PL Wijngaard**	Parsippany
FJ Raal	Johannesburg	**G Schwartz**	Denver	**JP Kastelein**	Amsterdam
W Koenig	Munich	**A Friedman**	Parsippany		

On behalf of the ORION Phase III investigators

ORION Phase III pooled analysis: Background and rationale

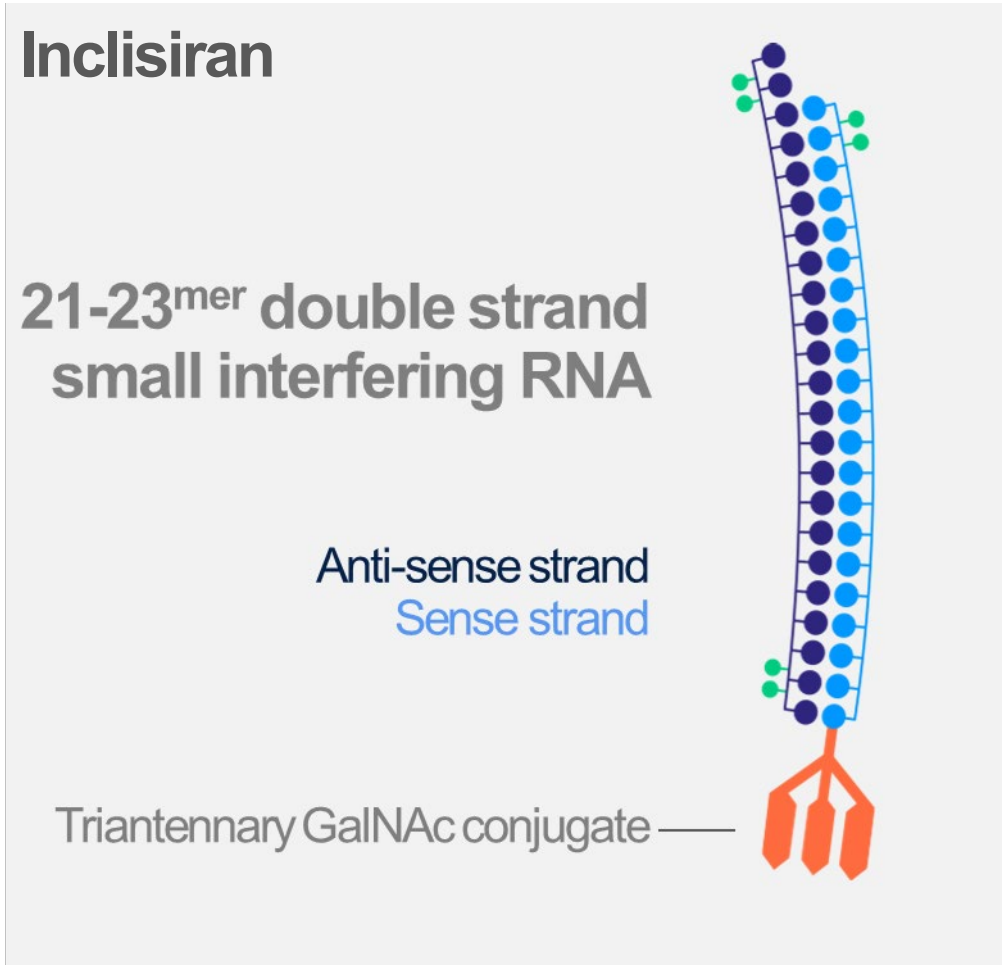
Challenges remain with regard to LDL-C lowering

LDL-C lowering is the most effective intervention to change the course of ASCVD and FH yet substantial residual risk remains despite aggressive treatment with statins and other agents[1].

- 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

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.

Online e-publications of ESC and AHA Individual Study presentations

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Leiter, M.D., Frederick J. Raal, Ph.D., Jenna A. Bisch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., and John J.P. Kastelein, M.D., Ph.D., for the ORION-10 and ORION-11 Investigators*

ABSTRACT

BACKGROUND

Inclisiran inhibits hepatic synthesis of proprotein convertase subtilisin–kexin type 9. Previous studies suggest that inclisiran might provide sustained reductions in low-density lipoprotein (LDL) cholesterol levels with infrequent dosing.

METHODS

We enrolled patients with atherosclerotic cardiovascular disease (ORION-10 trial) and patients with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent (ORION-11 trial) who had elevated LDL cholesterol levels despite receiving statin therapy at the maximum tolerated dose. Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days. The coprimary end points in each trial were the placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 and the time-adjusted percentage change in LDL cholesterol level from baseline after day 90 and up to day 540.

RESULTS

A total of 1561 and 1617 patients underwent randomization in the ORION-10 and ORION-11 trials, respectively. Mean (±SD) LDL cholesterol levels at baseline were 104.7±38.3 mg per deciliter (2.71±0.99 mmol per liter) and 105.5±39.1 mg per deciliter (2.73±1.01 mmol per liter), respectively. At day 510, inclisiran reduced LDL cholesterol levels by 52.3% (95% confidence interval [CI], 48.8 to 55.7) in the ORION-10 trial and by 49.9% (95% CI, 46.6 to 53.1) in the ORION-11 trial, with corresponding time-adjusted reductions of 53.8% (95% CI, 51.3 to 56.2) and 49.2% (95% CI, 46.8 to 51.6) (P<0.001 for all comparisons vs. placebo). Adverse events were generally similar in the inclisiran and placebo groups in each trial, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs. 0.9% in the ORION-10 trial and 4.7% vs. 0.5% in the ORION-11 trial); such reactions were generally mild, and none were severe or persistent.

CONCLUSIONS

Reductions in LDL cholesterol levels of approximately 50% were obtained with inclisiran, administered subcutaneously every 6 months. More injection-site adverse events occurred with inclisiran than with placebo. (Funded by the Medicines Company; ORION-10 and ORION-11 ClinicalTrials.gov numbers, NCT03399370 and NCT03400800.)

From the Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, London (K.K.R.); the Department of Cardiology, Mayo Clinic, Rochester, MN (R.S.W.); the Medicines Company, Zurich, Switzerland (D.K.); Deutsches Herzzentrum München, Technische Universität München, and Deutsches Zentrum für Herz-Kreislauf-Forschung (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, and the Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm — all in Germany (W.K.); Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.); the Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (F.J.R.); the Medicines Company, Parsippany, NJ (J.A.B., T.R., P.L.J.W.); Summit Analytical, Denver (M.J.), and the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam (J.J.P.K.). Address reprint requests to Dr. Ray at the Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, Reynolds Bldg., St. Dunstans Rd., London W6 8RP, United Kingdom, or at k.ray@imperial.ac.uk.

*A list of the ORION-10 and ORION-11 investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Ray and Wright contributed equally to this article.

This article was published on March 18, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa1912387

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia

Frederick J. Raal, M.D., Ph.D., David Kallend, M.B., B.S., Kausik K. Ray, M.D., M.Phil., Traci Turner, M.D., Wolfgang Koenig, M.D., R. Scott Wright, M.D., Peter L.J. Wijngaard, Ph.D., Danielle Curcio, M.B.A., Mark J. Jaros, Ph.D., Lawrence A. Leiter, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ORION-9 Investigators*

ABSTRACT

BACKGROUND

Familial hypercholesterolemia is characterized by an elevated level of low-density lipoprotein (LDL) cholesterol and an increased risk of premature atherosclerotic cardiovascular disease. Monoclonal antibodies directed against proprotein convertase subtilisin–kexin type 9 (PCSK9) have been shown to reduce LDL cholesterol levels by more than 50% but require administration every 2 to 4 weeks. In a phase 2 trial, a twice-yearly injection of inclisiran, a small interfering RNA, was shown to inhibit hepatic synthesis of PCSK9 in adults with heterozygous familial hypercholesterolemia.

METHODS

In this phase 3, double-blind trial, we randomly assigned, in a 1:1 ratio, 482 adults who had heterozygous familial hypercholesterolemia to receive subcutaneous injections of inclisiran sodium (at a dose of 300 mg) or matching placebo on days 1, 90, 270, and 450. The two primary end points were the percent change from baseline in the LDL cholesterol level on day 510 and the time-adjusted percent change from baseline in the LDL cholesterol level between day 90 and day 540.

RESULTS

The median age of the patients was 56 years, and 47% were men; the mean baseline level of LDL cholesterol was 153 mg per deciliter. At day 510, the percent change in the LDL cholesterol level was a reduction of 39.7% (95% confidence interval [CI], −43.7 to −35.7) in the inclisiran group and an increase of 8.2% (95% CI, 4.3 to 12.2) in the placebo group, for a between-group difference of −47.9 percentage points (95% CI, −53.5 to −42.3; P<0.001). The time-averaged percent change in the LDL cholesterol level between day 90 and day 540 was a reduction of 38.1% (95% CI, −41.1 to −35.1) in the inclisiran group and an increase of 6.2% (95% CI, 3.3 to 9.2) in the placebo group, for a between-group difference of −44.3 percentage points (95% CI, −48.5 to −40.1; P<0.001). There were robust reductions in LDL cholesterol levels in all genotypes of familial hypercholesterolemia. Adverse events and serious adverse events were similar in the two groups.

CONCLUSIONS

Among adults with heterozygous familial hypercholesterolemia, those who received inclisiran had significantly lower levels of LDL cholesterol than those who received placebo, with an infrequent dosing regimen and an acceptable safety profile. (Funded by the Medicines Company; ORION-9 ClinicalTrials.gov number, NCT03397121.)

From the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (F.J.R.); the Medicines Company, Zurich, Switzerland (D.K.); the Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College, London (K.K.R.); Medpace Reference Laboratories, Cincinnati (T.T.); Deutsches Herzzentrum München, Technische Universität München, and German Center for Cardiovascular Research, Munich Heart Alliance, Munich (W.K.), and the Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm (W.K.) — all in Germany; the Division of Preventive Cardiology and the Department of Cardiology, Mayo Clinic, Rochester, MN (R.S.W.); the Medicines Company, Parsippany, NJ (P.L.J.W., D.C.); Summit Analytical, Denver (M.J.J.); Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.); and the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam (J.J.P.K.) Address reprint requests to Dr. Raal at the Division of Endocrinology and Metabolism, Faculty of Health Sciences, University of the Witwatersrand, 7 York Rd., Parktown, Johannesburg 2193, South Africa, or at frederick.raal@wits.ac.za.

*A list of the ORION-9 investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 18, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa1913805

1. DOI: 10.1056/NEJMoa1912387

2. DOI: 10.1056/NEJMoa1913805

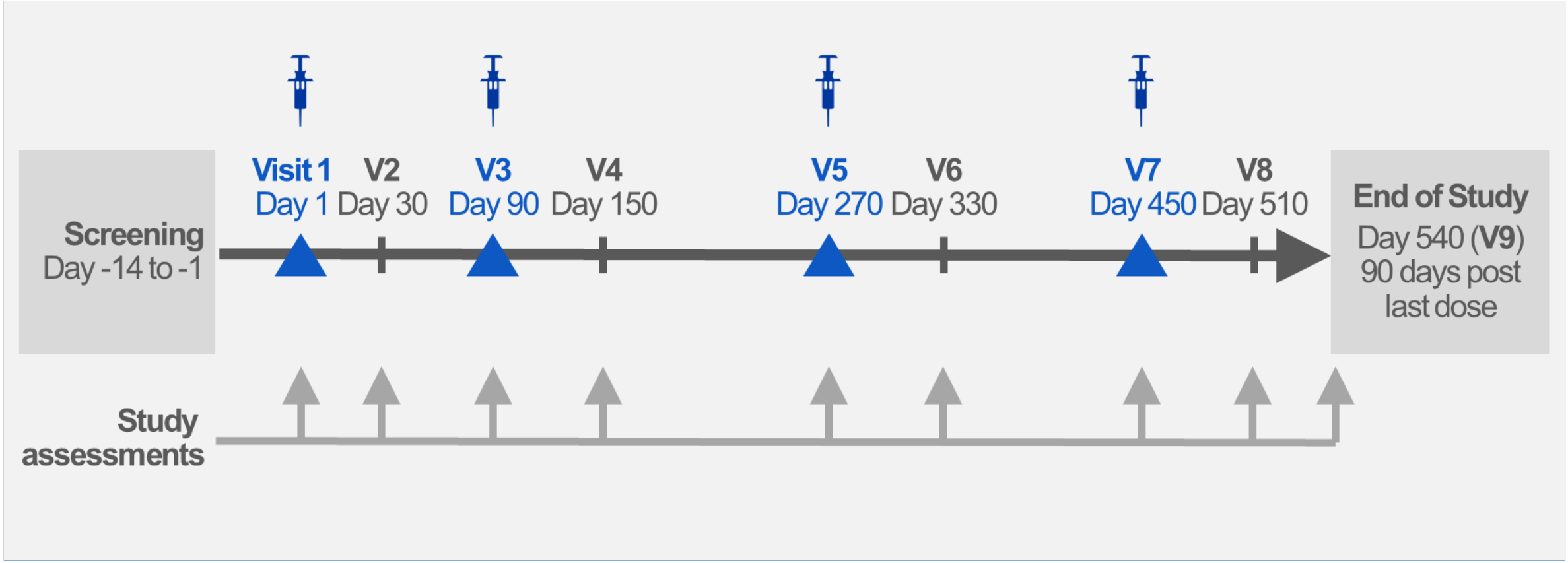
Purpose

To assess efficacy and safety of inclisiran 300 mg compared to placebo in a pooled analysis of all Phase III trials

ORION Phase III pooled analysis: Common study design

18 months treatment & observation

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



ORION Phase III pooled analysis: Entry criteria

General study inclusions and exclusions

Inclusion criteria	Exclusion criteria
Age ≥18 years	Prior or planned use of PCSK9 mAbs
Statin treatment	MACE within 3 months of randomization
Maximally tolerated doses, or documented intolerance	NYHA class IV HF — or LVEF 25%
Ezetimibe allowed	Uncontrolled severe hypertension
Informed consent required	Severe concomitant non CV disease
	Prior/planned other investigational drug
	Fasting TG >400 mg/mL (4.52mmol/L)

ORION Phase III pooled analysis: Entry criteria

Specific study inclusions

ORION-9	ORION-10	ORION-11
HeFH[1]	ASCVD (CHD, CVD, PAD)	ASCVD (CHD, CVD, PAD)
Stable on a low-fat diet		ASCVD risk equivalents • Type 2 diabetes • 10-year risk ≥20% • HeFH[1]
LDL-C ≥100 mg/dL	LDL-C ≥70 mg/dL	LDL-C ≥70 mg/dL

1. Diagnosed by genetic testing and/or Simon Broome criteria

ORION Phase III pooled analysis: 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 Phase III pooled analysis: Statistical plan

Large sample enrolled to enable reliable inference

Pre-specified pooling strategy and methods - agreed with regulatory agencies

Primary endpoints

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

Sensitivity analysis for primary efficacy endpoints

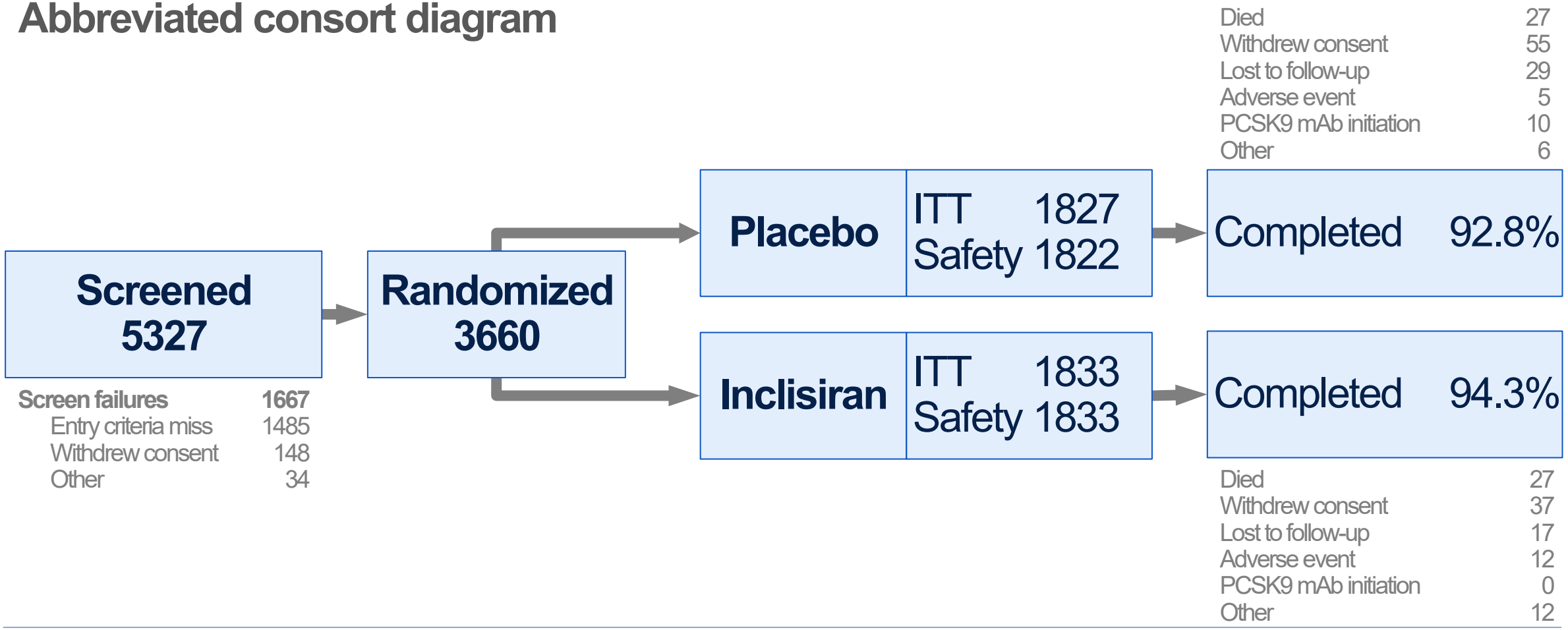
- Pre-specified imputation and analysis methods used to account for missing data

Safety observation of ~7000 inclisiran injections and >2700 years patient exposure

ORION Phase III pooled analysis: Patient disposition

High proportion of patients completed the studies

Abbreviated consort diagram



Safety population comprises any subject given any study medication

ORION Phase III pooled analysis: Patients

Representative high risk cohort balanced by randomization

Patient characteristic ITT population[1]	Placebo N = 1827		Inclisiran N = 1833	
Age median (range) - years	65	(21-89)	65	(20-90)
United States	812	(44%)	814	(44%)
Male gender	1244	(68%)	1226	(67%)
Diabetes	631	(35%)	687	(38%)
Lipid management treatment	1741	(95%)	1767	(96%)
Statins	1675	(92%)	1686	(92%)
Of which high intensity statins given	1345	(74%)	1356	(74%)
Ezetimibe	268	(15%)	246	(13%)
Baseline LDL-C mg/dL (SD)	111	(44)	112	(45)

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

ORION Phase III pooled analysis

Efficacy results

ORION Phase III pooled analysis: Efficacy

Highly significant lowering of LDL-C relative to placebo

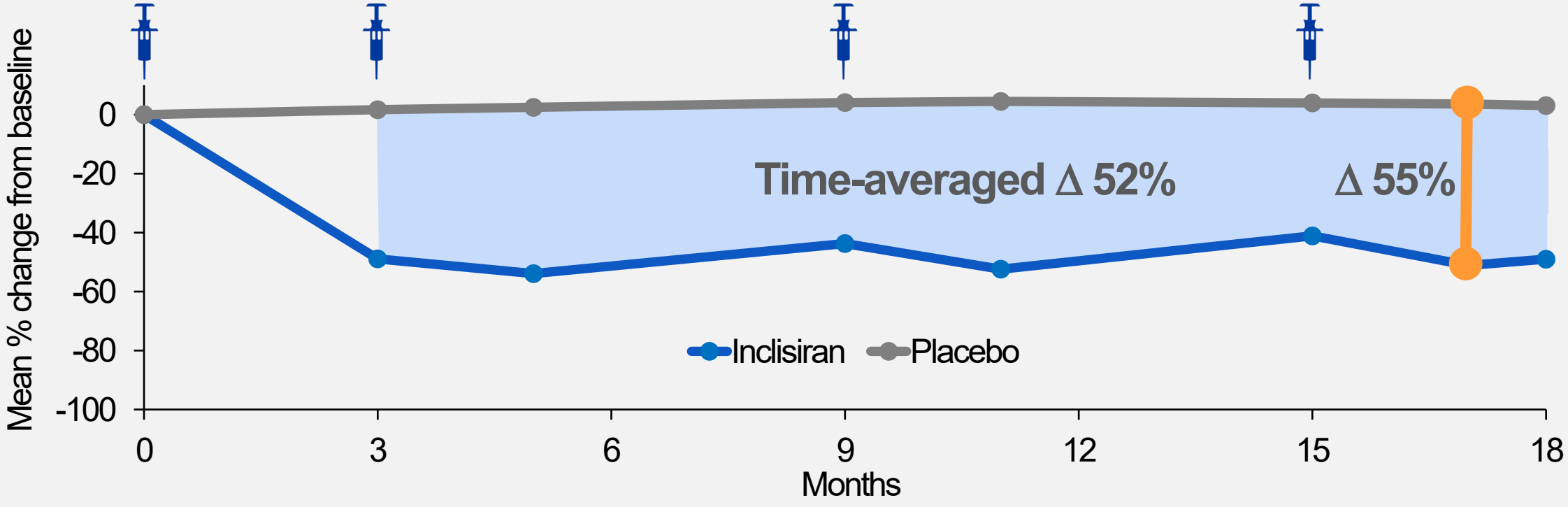
Treatment group	N (ITT[1])	Percent change LDL-C			
		Mean at day 510		Time-averaged day 90 - 540	
		Observed	Imputed[2]	Observed	Imputed[3]
Placebo	1833	+ 4	+ 6	+ 4	+ 5
Inclisiran	1827	- 51	- 45	- 49	- 45
Difference (1º endpoint)		**- 55**	**- 51**	**- 52**	**- 51**
P-value		**<0.0001**		**<0.0001**	

1. All patients who were randomized, analyzed according to randomization 2: Multiple imputation washout model 3: Control-based pattern mixed model

ORION Phase III pooled analysis: Efficacy

Durable and potent with consistent effect over 18 months

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



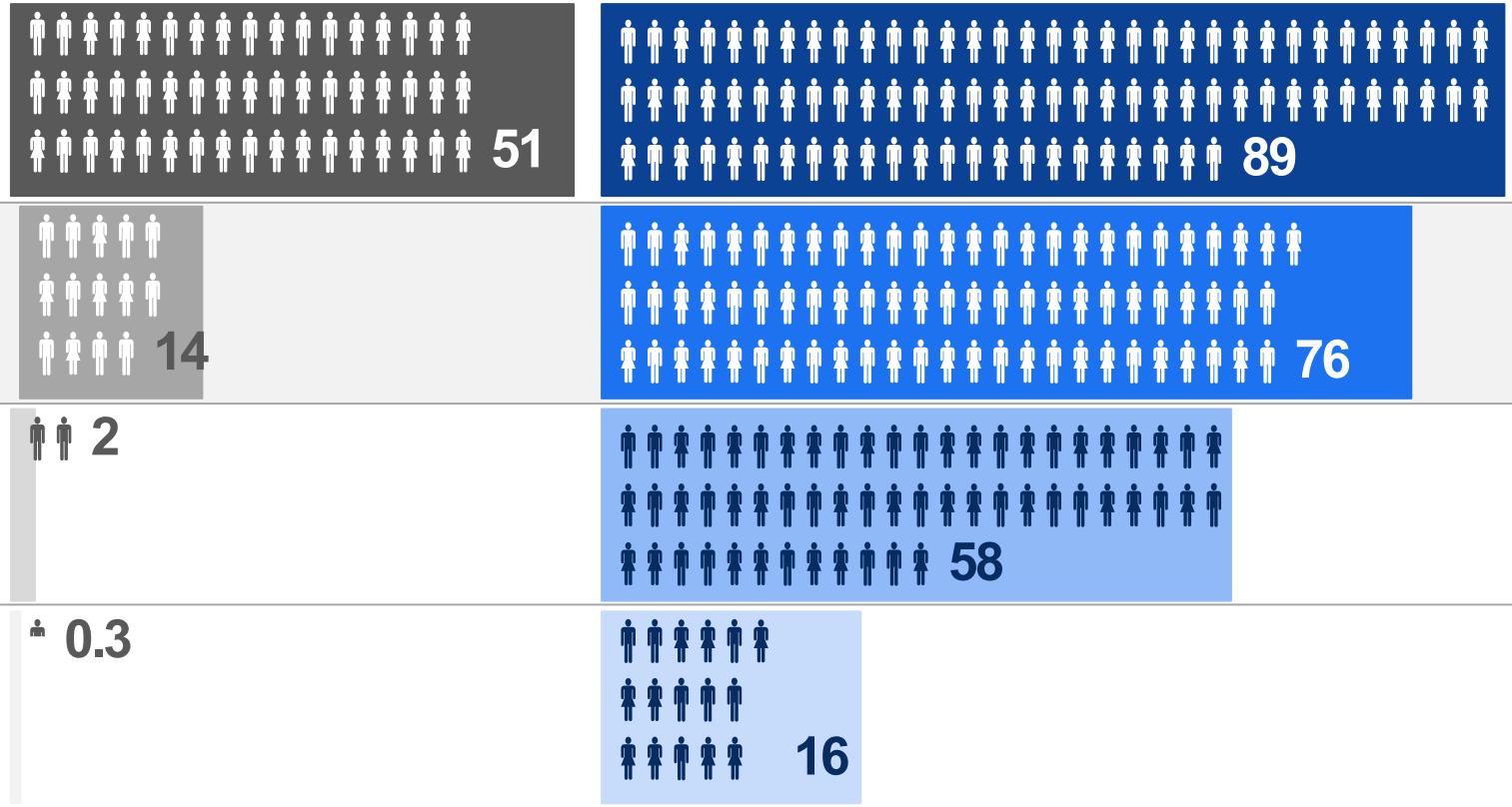
P-value for placebo – inclisiran comparison at each time point <0.0001

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

ORION Phase III pooled analysis: Efficacy

Likelihood of achieving specific LDL-C thresholds

LDL-C threshold	100 patients on statin	100 patients on statin + inclisiran	Odds ratio
<100 mg/dL	51	89	8
<70 mg/dL	14	76	**19**
<50 mg/dL	2	58	54
<25 mg/dL	0.3	16	60



Likelihood of reaching LDL-C thresholds at Day 510 among patients with available data

ORION Phase III pooled analysis: Efficacy

Effects on other lipid parameters

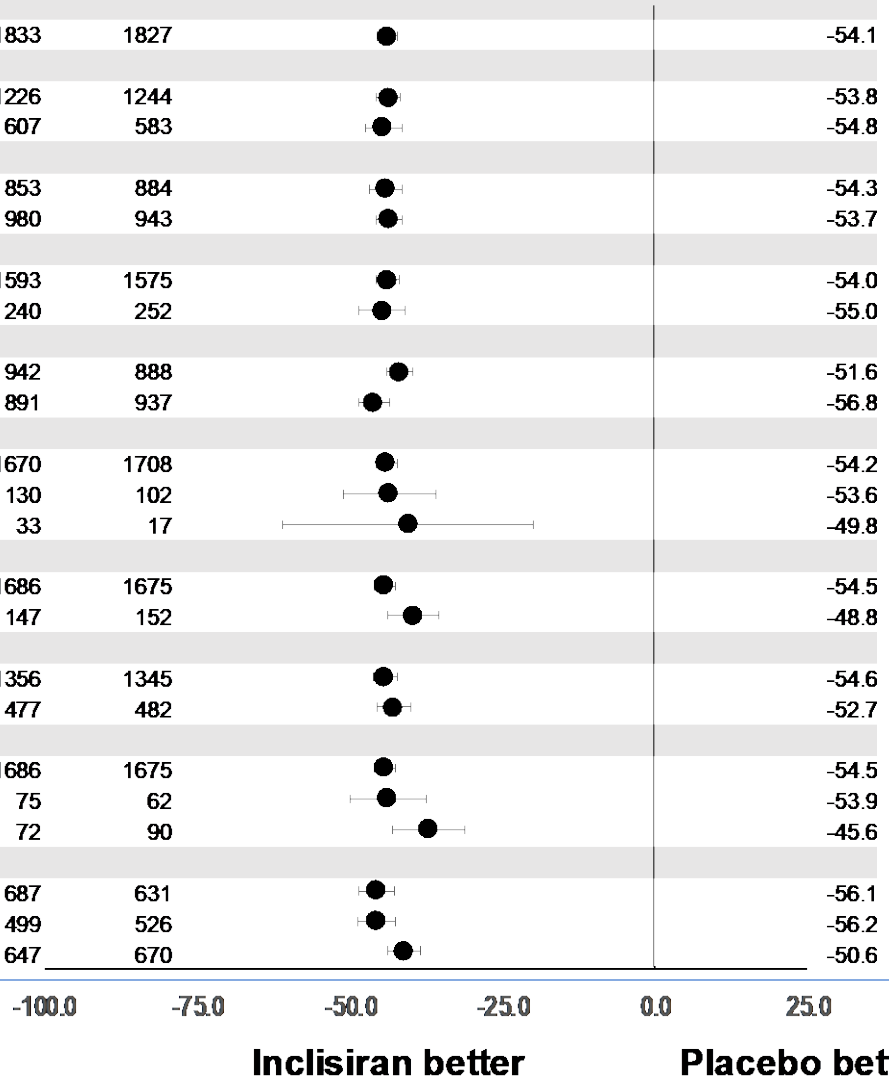
Percent Change from baseline to day 510 ITT population[1] Imputed values[2]		Placebo N = 1833	Inclisiran N = 1827	p-value
PCSK9	Mean %	+ 14.8	- 68.2	<0.0001
Total cholesterol	Mean %	+ 2.9	- 29.5	<0.0001
Non HDL-C	Mean %	+ 3.6	- 42.8	<0.0001
ApoB	Mean %	+ 1.7	- 40.2	<0.0001
Lp (a) (day 540)	Median %	+ 0.0	- 20.0	<0.0001[3]

1. All patients who were randomized 2: Imputed using a mixed model for repeated measures 3: Non-parametric test; not imputed

ORION Phase III pooled analysis: Efficacy

Robust ↓LDL-C across pre-specified sub-populations

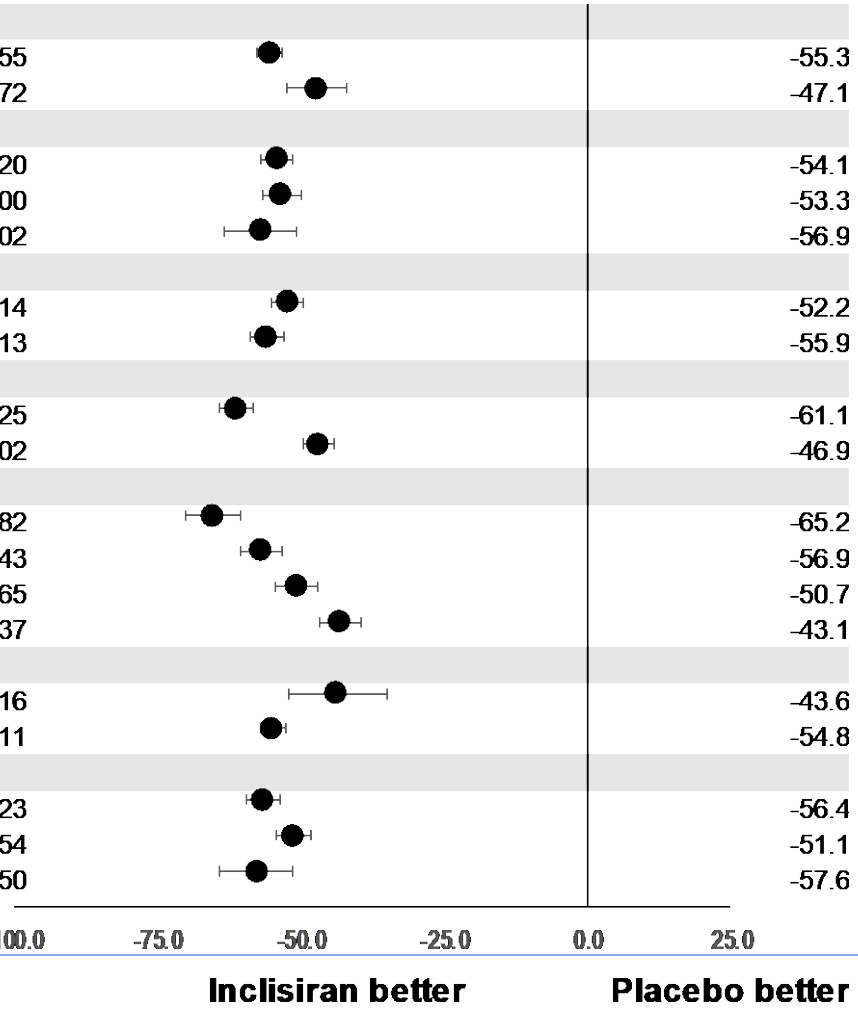
Subgroup	Inclisiran N	Placebo N	LS Mean Percent Difference in LDL-C
Overall			
Overall	1833	1827	-54.1
Sex			
Male	1226	1244	-53.8
Female	607	583	-54.8
Age <65 yr or ≥65 yr			
<65 yr	853	884	-54.3
≥65 yr	980	943	-53.7
Age <75 yr or ≥75 yr			
<75 yr	1593	1575	-54.0
≥75 yr	240	252	-55.0
Body mass index			
≤29.7	942	888	-51.6
>29.7	891	937	-56.8
Race			
White	1670	1708	-54.2
Black	130	102	-53.6
Other	33	17	-49.8
Baseline statin treatment			
On statin	1686	1675	-54.5
Not on statin	147	152	-48.8
Intensity of statin treatment			
High intensity statin	1356	1345	-54.6
Not on high intensity statin	477	482	-52.7
Lipid management treatment (LMT)			
Any statin	1686	1675	-54.5
Other LMT but no statin	75	62	-53.9
No LMT	72	90	-45.6
Metabolic disease			
Diabetes	687	631	-56.1
Metabolic syndrome	499	526	-56.2
Neither	647	670	-50.6



ORION Phase III pooled analysis: Efficacy

Robust ↓LDL-C across pre-specified sub-populations

Subgroup	Inclisiran N	Placebo N	LS Mean Percent Difference in LDL-C
Risk category			
ASCVD	1552	1555	-55.3
ASCVD equivalent	281	272	-47.1
Renal function (eGFR - Cockcroft Gault)			
Normal	996	1020	-54.1
Mild impairment	637	600	-53.3
Moderate impairment	196	202	-56.9
Baseline triglycerides in mg/dL			
≤130	918	914	-52.2
>130	915	913	-55.9
Baseline LDL-C in mg/dL			
≤100	927	925	-61.1
>100	906	902	-46.9
Baseline LDL-C quartiles in mg/dL			
≤82	455	482	-65.2
>82 - ≤100	472	443	-56.9
>100 - ≤129	434	465	-50.7
>129	472	437	-43.1
Ethnicity			
Hispanic or latino	120	116	-43.6
Not hispanic or latino	1713	1711	-54.8
Geographic region			
North America	826	823	-56.4
Europe	859	854	-51.1
South Africa	148	150	-57.6



ORION Phase III pooled analysis

Safety results

ORION Phase III pooled analysis: Safety and tolerability

Adverse event profile similar to placebo

Treatment emergent adverse event (TEAE) Safety population[1] – AEs in ≥5% patients[2]	Placebo N = 1822		Inclisiran N = 1833	
Patients with at least one TEAE	1409	(77.3%)	1430	(78.0%)
Diabetes mellitus adverse events	207	(11.4%)	212	(11.6%)
Nasopharyngitis	134	(7.4%)	140	(7.6%)
Upper respiratory tract infection	103	(5.7%)	105	(5.7%)
Hypertension	104	(5.7%)	104	(5.7%)
Arthralgia	72	(4.0%)	91	(5.0%)
Protocol-defined injection site TEAE	12	(0.7%)	91	(5.0%)

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 Phase III pooled analysis: Safety and tolerability

No evidence of liver, kidney, muscle or platelet toxicity

Laboratory tests Safety population[1,2]		Placebo N = 1822		Inclisiran N = 1833	
Liver function	ALT >3x ULN	7	(0.4%)	9	(0.5%)
	AST >3x ULN	10	(0.5%)	8	(0.4%)
	ALP >2x ULN	5	(0.3%)	8	(0.4%)
	Bilirubin >2x ULN[3]	14	(0.8%)	14	(0.8%)
Kidney function	Creatinine >2 mg/dL	39	(2.1%)	36	(2.0%)
Muscle	CK >5x ULN	22	(1.2%)	24	(1.3%)
	CK >10x ULN	6	(0.3%)	4	(0.2%)
Hematology	Platelet count ≤75x10^9/L	2	(0.1%)	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 Phase III pooled analysis: Exploratory endpoint

Serious adverse events and CV endpoint

Serious treatment emergent adverse events Safety population[1,2]	Placebo N = 1822		Inclisiran N = 1833	
Patients with at least one serious TEAE	**419**	**(23.0%)**	**374**	**(20.4%)**
All cause death	27	(1.5%)	27	(1.5%)
Cancer	6	(0.3%)	4	(0.2%)
New, worsening or recurrent malignancy	49	(2.7%)	44	(2.4%)
TEAEs leading to drug discontinuation	**35**	**(1.9%)**	**45**	**(2.5%)**
Pre-specified exploratory CV endpoint[3]	**172**	**(9.4%)**	**131**	**(7.1%)**
Cardiovascular death	14	(0.8%)	17	(0.9%)
Resuscitated cardiac arrest	1	(0.1%)	4	(0.2%)
Non-fatal MI	142	(7.8%)	96	(5.2%)
Stroke (Ischemic or Hemorrhagic)	18	(1.0%)	16	(0.9%)

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 Phase III pooled analysis: Summary

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

Efficacy

- Primary and secondary endpoints were met
  - Primary endpoint: ↓55% (observed values) and 51% (imputed) reduction at 17 months
  - Secondary endpoint ↓52% (observed) and 51% (imputed) reduction 3-18 months
  - Reductions were consistent across sub-populations
  - Accompanied by substantial lowering of PCSK9, non-HDL-C, apoB and Lp(a)

Safety and tolerability

- Inclisiran safety profile was similar to placebo
- No adverse changes in laboratory markers

Exploratory basket of CV events less frequent on inclisiran than placebo

Conclusions and implications

Inclisiran is a novel approach to reduce the level of LDL-C

- With twice yearly administration, it provides robust and durable LDL-C reduction over 18 months on top of maximally tolerated oral therapies.
- Effects were consistent in patients with HeFH, ASCVD, or ASCVD risk-equivalence.
- The safety profile was similar to placebo in a high risk population.

Twice yearly administration will coincide with typical twice yearly patient visits with health care providers, thereby assuring treatment adherence.

Thank you