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# ORION-9

## Inclisiran for heterozygous familial hypercholesterolemia

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**On behalf of the ORION-9 investigators**

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# ORION-9: Acknowledgements

## Contributions from 46 sites in 8 countries



### Lead enrolling investigators

|                       |  |                                     |
|-----------------------|--|-------------------------------------|
| <b>Canada</b>         | Jean Bergeron                            | Daniel Gaudet                       |
| <b>Czech Republic</b> | Victor Adamkova                          | Lucie Solcova                       |
| <b>Denmark</b>        | Erik Schmidt                             | Ib Christian Clausen                |
| <b>Netherlands</b>    | Frank Visseren                           | Erik Stroes                         |
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| <b>Spain</b>          | Jose Luis Diaz Diaz<br>Xavier Pinto Sala | Daniel Zambon Rados                 |
| <b>Sweden</b>         | Mats Eriksson                            | Stefano Romeo                       |
| <b>United States</b>  | Traci Turner                             | John Homan                          |

# ORION-9: Background and rationale

## HeFH highly prevalent and clinically challenging

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**A genetic disorder affecting 1 in 250 or ~30 million people worldwide<sup>1</sup>**

- 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<sup>2</sup>**

- 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<sup>3</sup>

**Management is primary prevention of ASCVD through LDL-C lowering therapy<sup>4,5,6</sup>**

- High intensity statins  $\pm$  ezetimibe  $\pm$  monoclonal antibodies against PCSK9

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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 2013;381:1293-301

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



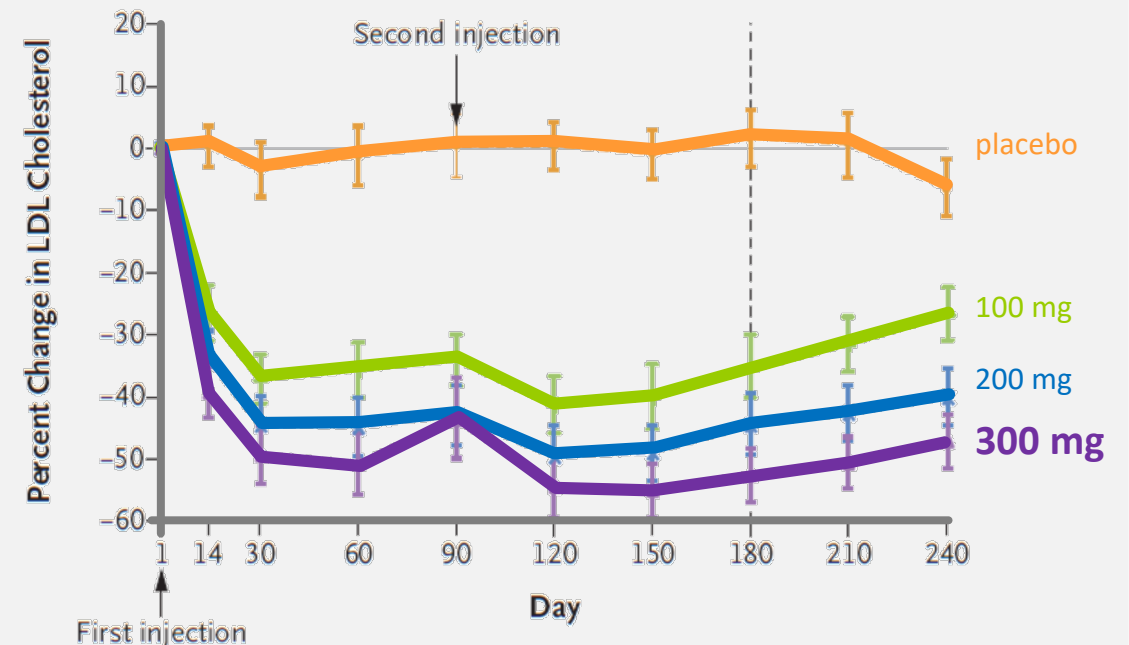
Inclisiran is a small interfering double-stranded RNA<sup>1</sup>

- Harnesses natural process of RNAi in liver

Dose-finding<sup>2</sup> and PD modeling<sup>3</sup> 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



### 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



### Inclusion criteria

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Age  $\geq$ 18 years

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HeFH diagnosed by genetic testing and/or Simon Broome criteria<sup>1</sup>

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LDL-C  $\geq$ 100 mg/dL (2.6 mmol/L)

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Stable on a low-fat diet

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Maximally tolerated statin doses

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Ezetimibe allowed

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Informed consent

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### Exclusion criteria

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Prior (90d) or planned use of PCSK9 mAbs

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MACE within 3 months of randomization

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NYHA class III-IV HF — or LVEF 30%

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Uncontrolled severe hypertension

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Severe concomitant non CV disease

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Fasting TG  $>$ 400 mg/mL (4.52 mmol/L)

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Pregnant, nursing or without contraception

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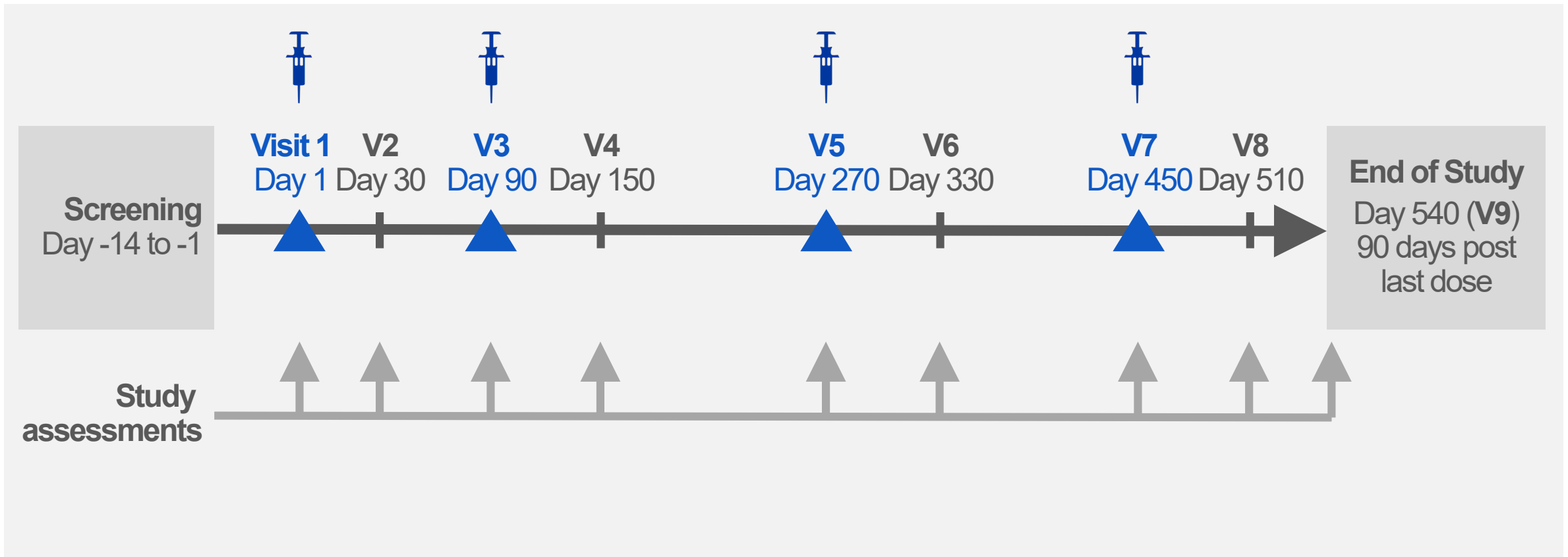
1. BMJ. 1991; 303: 893–896.

# 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

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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
- 2<sup>o</sup> and 3<sup>o</sup> analysis with commercial bioinformatics software
- Variants aligned to GRCh37/hg19 reference genome; classified by current guidelines<sup>1,2</sup>

### LDLR variants grouped

- Pathogenic
- Likely pathogenic
- Uncertain significance

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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





**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  $\alpha = 0.025$

**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**

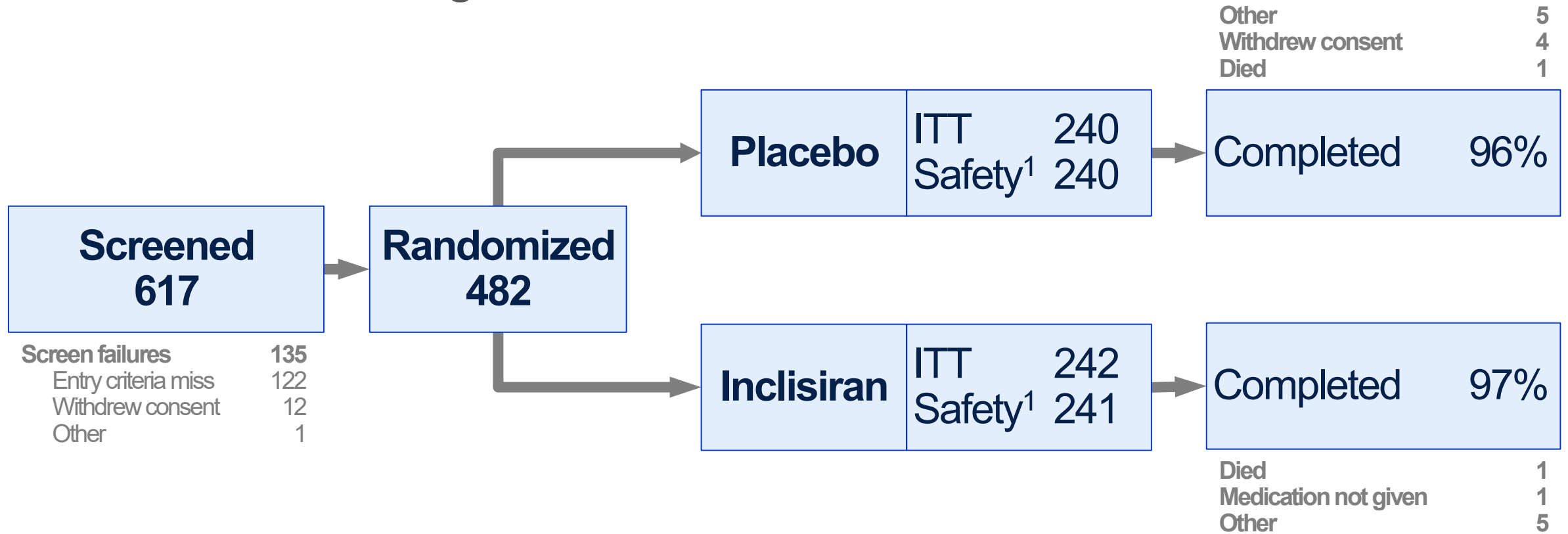
**Pre-specified sub-group analyses by FH genotype**

# 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



| Patient characteristic                        | Placebo         | Inclisiran      |
|---|-----------------|-----------------|
| ITT population <sup>1</sup>                   | 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%)        |
| <b>Lipid management treatment</b>             |                 |                 |
| Statins                                       | 217 (90%)       | 219 (91%)       |
| Of which high intensity statins given         | 171 (79%)       | 185 (84%)       |
| Ezetimibe use                                 | 135 (56%)       | 120 (50%)       |
| <b>Baseline LDL-C mg/dL (±SD)<sup>2</sup></b> | <b>155 (58)</b> | <b>151 (50)</b> |

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



| Genetic variants               | Placebo |       | Inclisiran |        |
|--------------------------------|---------|-------|------------|--------|
| ITT population <sup>1</sup>    | 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



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# **Efficacy results**

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

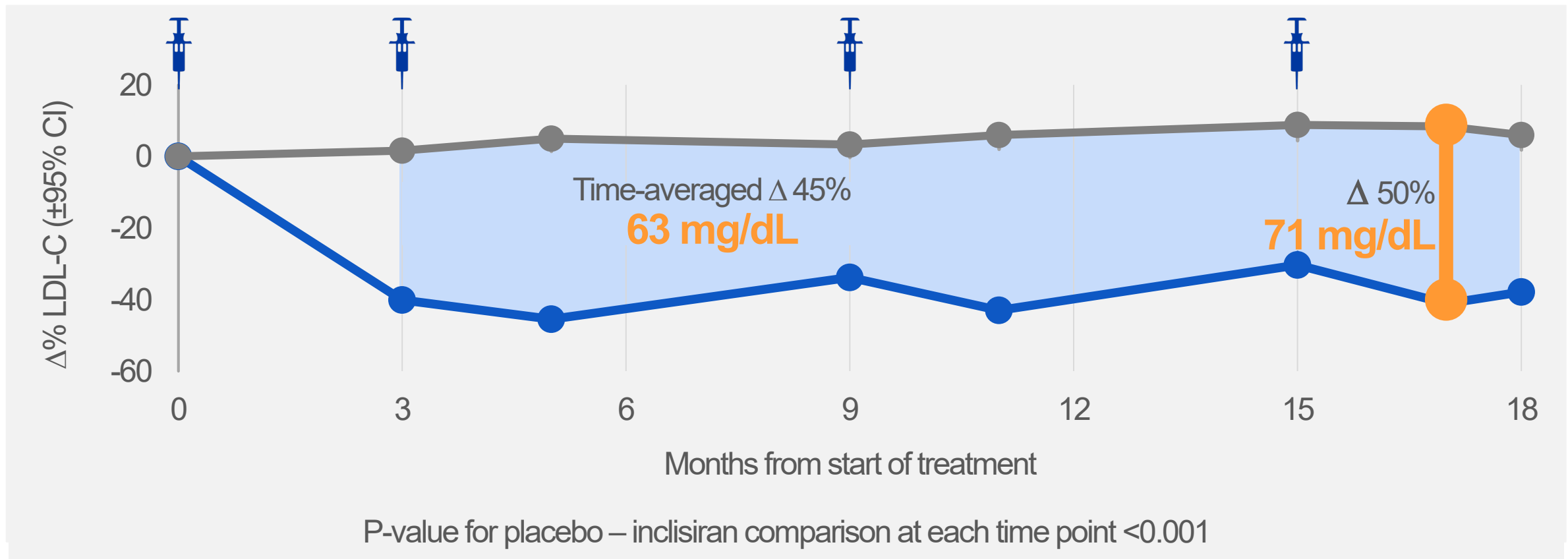
1. A wash-out model was used to account for missing data  
 2. A pattern mixed model was used to account for missing data

# ORION-9: Efficacy

## Durable and potent effect over 18 months



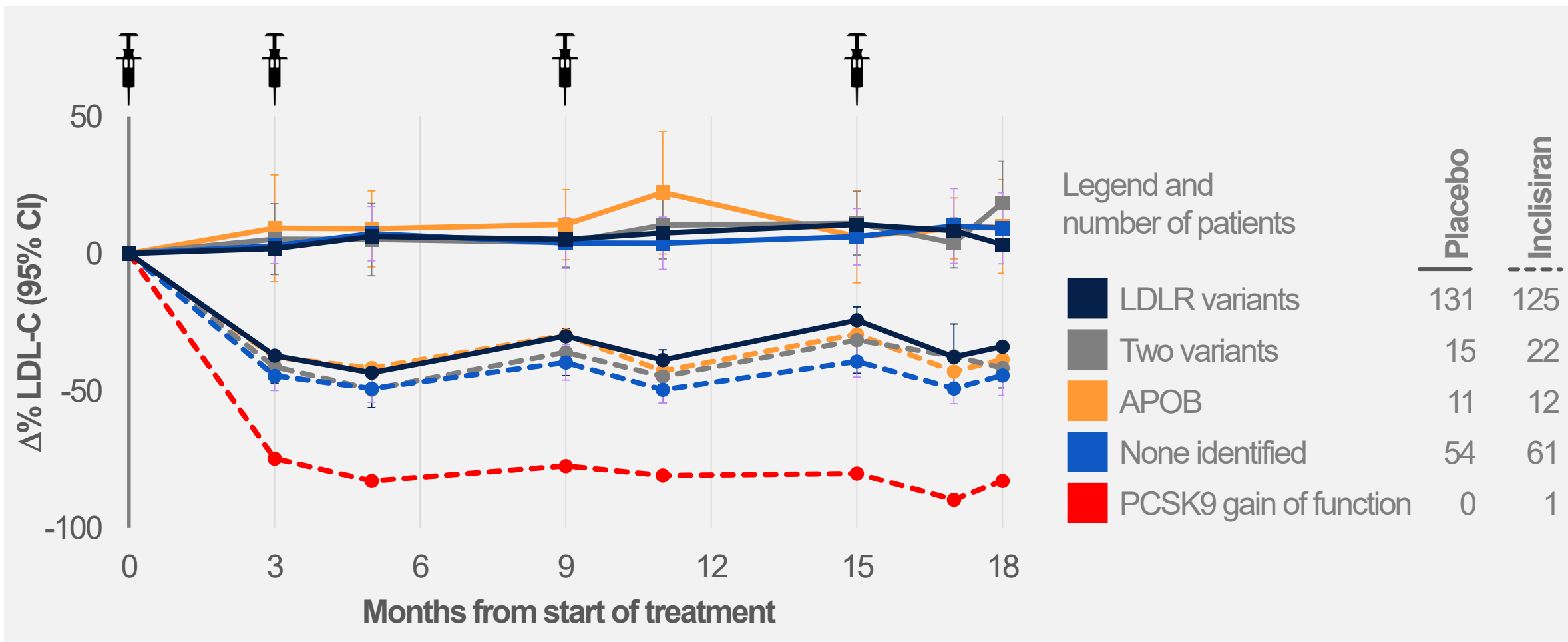
### Percent and absolute change in LDL-C over time – observed values in ITT patients



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

# ORION-9: Efficacy

## Change in LDL-C by genetic variants







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# Safety results

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# ORION-9: Safety and tolerability

## Safety profile similar to placebo



| <b>Treatment emergent adverse event (TEAE)</b><br>Safety population <sup>1</sup> – AEs in ≥5% patients | <b>Placebo</b><br>N = 240 | <b>Inclisiran</b><br>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



| TEAEs at injection site                                | Placebo  |               | Inclisiran |                | Δ            |
|--|----------|---------------|------------|----------------|--------------|
| Safety population <sup>1</sup>                         | N = 240  |               | N = 241    |                |              |
| <b>Protocol-defined event</b>                          | <b>1</b> | <b>(0.4%)</b> | <b>33</b>  | <b>(13.7%)</b> | <b>13.3%</b> |
| (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



| <b>Laboratory tests</b>          |                                       | <b>Placebo</b> |        | <b>Inclisiran</b> |        |
|----------------------------------|---------------------------------------|----------------|--------|-------------------|--------|
| Safety population <sup>1,2</sup> |                                       | N = 240        |        | N = 241           |        |
| <b>Liver function</b>            | 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 <sup>3</sup>        | 3              | (1.2%) | 4                 | (1.7%) |
| <b>Kidney function</b>           | Creatinine >2 mg/dL                   | 1              | (0.4%) | 1                 | (0.4%) |
| <b>Muscle</b>                    | CK >5x ULN                            | 5              | (2.1%) | 4                 | (1.7%) |
| <b>Hematology</b>                | Platelet count <75x10 <sup>9</sup> /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



| <b>Serious TEAEs</b>                                     | <b>Placebo</b> |                | <b>Inclisiran</b> |               |
|--|----------------|----------------|-------------------|---------------|
| Safety population <sup>1,2</sup>                         | N = 240        |                | N = 241           |               |
| <b>Patients with at least one serious TEAE</b>           | <b>33</b>      | <b>(13.8%)</b> | <b>18</b>         | <b>(7.5%)</b> |
| 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%)        |
| <b>Pre-specified exploratory CV endpoint<sup>3</sup></b> | <b>10</b>      | <b>(4.2%)</b>  | <b>10</b>         | <b>(4.2%)</b> |

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



**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**

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