

Two Phase 3 trials of inclisiran in patients with elevated LDL cholesterol

Ray, KK et al. *N Engl J Med.* 2020;382(16):1507–1519

Background

PCSK9 binding in the circulation by monoclonal antibodies reduces both LDL-C levels and the incidence of cardiovascular events

Inclisiran is a small interfering RNA therapeutic agent that reduces hepatic synthesis of PCSK9

In both the ORION-10 and ORION-11 clinical trials, **inclisiran shows promise** in managing people with **statin-refractory hypercholesterolaemia**



Aim: To assess the efficacy, safety and adverse-event profile of inclisiran (a PCSK9 inhibitor) in patients at high risk for cardiovascular disease in whom LDL-C levels were elevated despite receiving statin therapy at the maximum tolerated dose with or without additional lipid-lowering therapy

Methods

Randomised, double-blind, placebo-controlled, parallel-group, Phase 3 trials

ORION-10

Adults with **ASCVD** and **LDL-C 70 mg/dL** (1.8 mmol/L) or higher
1,561 participants

ORION-11

Adults with **ASCVD** and **LDL-C 70 mg/dL** (1.8 mmol/L) or higher, or **ASCVD risk equivalent*** and **LDL-C 100 mg/dL** (2.6 mmol/L) or higher
1,617 participants

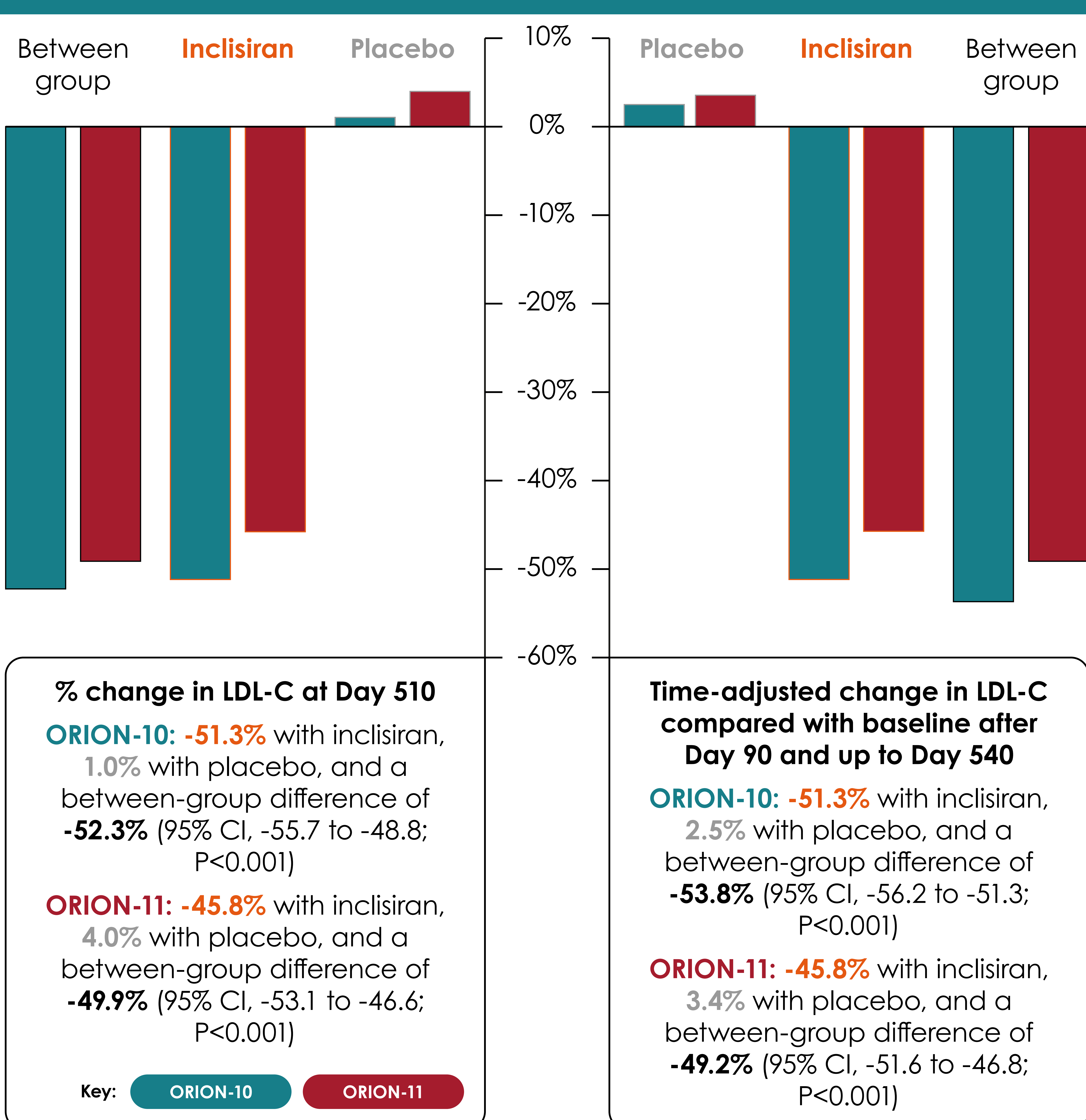
Receiving statin therapy at the maximum tolerated dose

Randomly assigned 1:1 to receive either **inclisiran (284 mg)** or **placebo SC injection** on Day 1, Day 90, Day 270 and Day 450 with an end-of-trial visit at Day 540

Inclisiran ITT pop.
ORION-10: **781**
ORION-11: **810**

Placebo ITT pop.
ORION-10: **780**
ORION-11: **807**

Results



Safety†

- Most AEs reported in both trials were **mild or moderate**
- The most common AEs **occurred in similar frequency** in both the **inclisiran** and **placebo** groups in both **ORION-10** and **ORION-11**
- Injection-site adverse events were **more frequent with inclisiran** than with **placebo**, but most were **mild or moderate**, did not require intervention and were not persistent
- SAEs were reported in **22.4% and 26.3% of patients in ORION-10**, and **22.3% and 22.5% in ORION-11**, in **inclisiran** and **placebo** groups respectively
- There were **12 deaths in the inclisiran** group and **11 in the placebo** group in **ORION-10**
- There were **14 deaths in the inclisiran** group and **15 in the placebo** group in **ORION-11**

Takeaways

Sustained reductions in LDL-C levels are achievable with an infrequent dosing schedule of inclisiran

Administration of inclisiran every 6 months is feasible and can significantly reduce LDL-C levels by approximately 50%

Abbreviations: AE, adverse event; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; ITT, intent to treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin-kexin type 9; pop., population; RNA, ribonucleic acid; SAE, serious adverse event; SC, subcutaneous.

Footnotes:

*Type 2 diabetes, familial hypercholesterolaemia, or a 10-year risk of a cardiovascular event of $\geq 20\%$ as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent.

†In ORION-10, 2 patients assigned to the placebo group did not receive placebo; therefore, there were 781 patients (inclisiran) and 778 patients (placebo) in the safety population. In ORION-11, 2 patients assigned to the placebo group did not receive placebo, and 1 patient assigned to placebo was given a dose of inclisiran in error and is included in the inclisiran group for safety reporting; therefore, there were 811 patients exposed to inclisiran and 804 patients exposed to placebo in the safety population.

References: Ray, K.K. et al. *N Engl J Med.* 2020;382(16):1507–1519

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