Inclisiran Phase III Pivotal Trials

AN OVERVIEW OF THE CLINICAL PROGRAM

ORION is a comprehensive clinical research program for inclisiran, the first and only small interfering RNA (siRNA) treatment that has demonstrated effective and sustained lowering of low-density lipoprotein cholesterol (LDL-C) with a safety profile similar to placebo.

12 clinical trials involving a broad patient population in 20 countries, including the United States, Canada, the United Kingdom, Germany, Spain, the Netherlands, Sweden and Denmark[1]

12 trials

20 countries

more than **500** sites

more than **22,000** patients

PHASE III PIVOTAL TRIALS: ORION-9, ORION-10 AND ORION-11

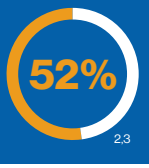
The ORION-9, -10 and -11 trials are multicenter, double-blind, randomized, placebo-controlled, 18-month studies[2,3].

About 3,600 patients were randomized to receive either placebo or inclisiran 284 mg treatment in addition to maximally tolerated statins with or without other lipid-lowering therapy. Patients received an initial dose of inclisiran or placebo via subcutaneous injection, another at 3 months and again every 6 months[2,3].

Primary endpoints were met in all three trials: percentage change in LDL-C from baseline to 17 months compared with placebo and time-adjusted percentage change in LDL-C from baseline between 3 months and up to 18 months[2,3].

STUDY RESULTS

Inclisiran showed effective and sustained LDL-C reduction of **up to**



ORION-9	ORION-10	ORION-11
LDL-C was reduced by 48% at 17 months with a time-adjusted reduction of 44% over 18 months[3]	**LDL-C was reduced by 52% at 17 months** with a time-adjusted reduction of 54% over 18 months[2]	**LDL-C was reduced by 50% at 17 months** with a time-adjusted reduction of 49% over 18 months[2]
• 482 patients with clinical or genetic evidence of heterozygous familial hypercholesterolemia	• 1561 patients with atherosclerotic cardiovascular disease (ASCVD)	• 1617 patients with ASCVD or ASCVD risk equivalents
• 46 sites	• 145 sites	• 70 sites
• 8 countries (including the United States, Canada and Spain)	• Study was conducted in the United States	• 7 countries (including the United Kingdom and Germany)

SAFETY

Inclisiran was well tolerated, with a safety profile shown to be comparable to placebo. The most common adverse reactions reported* were injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity and dyspnea. Adverse events at the injection site were generally mild and none were severe or persistent[2,3].

LONG-TERM OUTCOMES

Experts recognize that there is a consistent, linear relationship between LDL-C and cardiovascular risk:

- Every 1 mmol/L reduction in LDL-C should result in a 20% reduction in coronary heart disease mortality and a 10% reduction in total mortality over a period of 5 years[4]
- This relationship is reflected in international clinical treatment guidelines as well[5]

Novartis is currently conducting a Phase III 5 year trial, which aims to recruit 15,000 patients in the United Kingdom and the United States to study the impact of inclisiran on CV outcomes, including patient mortality.

* defined as ≥3% of patients treated with inclisiran and occurring more frequently than placebo

References

1. Novartis data on file. September 2020.
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3. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. *N Engl J Med.* 2020;382(16):1520–1530;
4. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376(9753):1670–1681;
5. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk. *Eur Heart J.* 2020;1(41):111–188.

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