NOVARTIS

Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial

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Introduction

Lowering low-density lipoprotein cholesterol (LDL-c) is already an established and effective pharmacological approach to reduce the risk of Atherosclerotic Cardiovascular Disease (ASCVD). Guidelines recommend risk-based LDL-c goals in order to maintain lower long-term LDL-c concentrations for those patients at higher risk of future ASCVD-related events.

Statin monotherapy achieves only 20-40% of very high-risk recommended LDL-c goals. Therefore, for these patients, not only combination therapy is recommended, but also drugs that improve adherence to treatment. New therapies target proprotein convertase subtilisin/kexin type 9 (PCSK9). The most common are monoclonal antibodies (mAb). These require subcutaneous injections every 2 weeks, which is equivalent to 26 injections per year; and have been shown to be safe in the long term and to reduce cardiovascular (CV) events. More recently, inclisiran, a small interfering ribonucleic acid (siRNA) has emerged. It degrades PCSK9 mRNA in the liver, inhibiting its translation and thus eliminating PCSK9 in the circulation. Its dosage allows two injections per year and has been shown to be well tolerated up to 18 months in the ORION-9, ORION-10 AND ORION-11 trials.

This study, ORION-3, is intended to evaluate the effect of long-term dosing of inclisiran in patients with high CV risk and elevated LDL-c.

Methods

ORION-3 is the open-label, multicenter, long-term (4-year) extension study of the ORION-1 study conducted across 52 study sites in 5 countries. ORION-1 was a phase II, multicenter, 1-year, double-blind, placebo-controlled, dose-finding study of inclisiran.

Patients had or were at high risk of Atherosclerotic Cardiovascular Disease (ASCVD); defined as either type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event >20%. Their LDL-c levels were elevated despite maximally tolerated statins or other lipid-lowering therapy.

Patients enrolled in ORION-1 who received inclisiran sodium (100 mg, 200 mg, or 300 mg in two doses; or 200 mg, 300 mg, or 500 mg in a single dose) were upgraded to receive 300 mg of inclisiran sodium in ORION-3. Inclisiran sodium was administered subcutaneously by a healthcare professional (inclisiran-only arm) on days 1, 180, 360, 540, 720, 810, 990, 1170, and 1350. Patients who received placebo in ORION-1, received 140 mg of evolocumab (mAb), 1 dose every 2 weeks self-administered subcutaneously, for up to 1 year, followed by transition to inclisiran sodium 300 mg subcutaneously for the remainder of the study (switching arm).

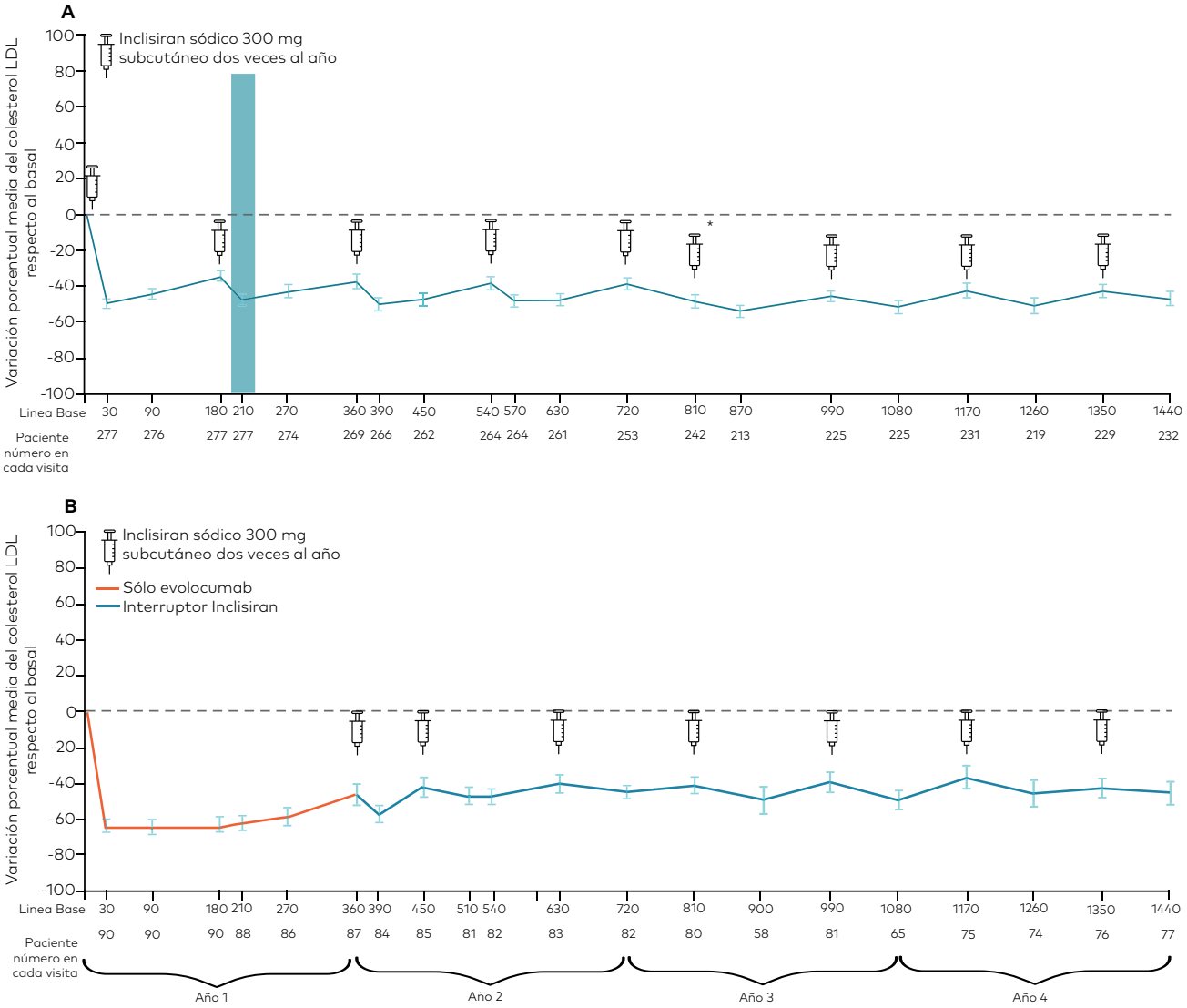
Results

Mean percentage change in LDL-c. (A) from ORION-1 baseline to day 1440 (4 years) of ORION-3 (inclisiran-only arm), and from (B) ORION-3 baseline to day 1440 (4 years) of ORION-3 (switching arm).

Inclisiran-only arm:
LDL-c concentrations at Day 210 were 1.56 (95% CI -1.68 to -1.44) mmol/L, reflecting a reduction of 47.5% (95% CI -50.7 to -44.3; p<0 0001) at approximately day 570, that is, after receiving the first dose in the ORION-1 study.

At 4 years, the change in the mean percentage ranged between -34.3% and -53.8%, with an overall 4-year time-averaged reduction of 44.2% through 9 injections. The mean absolute change ranged between -1.13 mmol/L and -1.76 mmol/L. LDL-c <1.3 mmol/L were achieved in 62% of the population.

The mean percentage change in PCSK9 concentrations ranged between –62.2% and –77.8% over the 4 years; already at 30 days of study it was reduced to –71.8% and at 1440 days it continued with -69.5%.



En la rama solo inclisirán, se toma el valor basal del estudio de ORION-1 para calcular el cambio porcentual medio
*D810 la inyección se administró como un intervalo de dosis único de 90 días según el diseño del estudio inicial con fines exploratorios

Switching arm:

Treatment with evolocumab during the first year, with a total of 25 injections, reduced LDL-c levels by an ave rage of 61%. After switching to inclisiran for the next 3 years, with a total of 7 injections, the mean reduction in LDL-c levels was 45.3%.

LDL-c concentrations and PCSK9 reductions on inclisiran were generally similar over the 3 years of the open study in both arms. Changes in other lipid parameters were also similar. It is only observed, in the switching arm, that the proportion of patients achieving >50% lowering of LDL-c was higher during evolocumab treatment.

Adverse events (AEs)

AEs at the injection site ocurred in 8.2% and 1.8% of inclisiran and placebo patients, respectively, in the pivotal studies. The proportion of patients in each group who discontinued treatment due to adverse reactions at the injection site was 0.2% and 0.0%, respectively. All of these adverse reactions were mild or moderate in severity, transient and resolved without sequelae. The most frequently ocurring adverse reactions at the injection site in patients treated with inclisiran were injection site reaction (3.1%), injection site pain (2.2%), injection site erythema (1.6%), and injection site rash (0.7%).

Discussion

Inclisiran twice yearly reduced sustained LDL-c and PCSK9 levels and was well tolerated up to 4 years. The results obtained in this open study are consistent with those of the 18-month placebo-controlled clinical trials. Similar results were obtained in the inclisiran-only arm and in the switching arm. This fact suggests that treatment with evolocumab did not alter the efficacy of inclisiran.

The guidelines update in 2019 recommends lowering LDL-c levels to ≤1.4 mmol/L. In this study, more than 60% of patients achieved that goal.

Injection site AEs did not worsen over time and resolved without sequelae. The hepatic AEs were consistent with those reported previously in the phase III trials.

Combining therapies that lower free PCSK9 and increase LDL receptors can decrease LDL-c levels by 75-80%. Evolocumab achieved a 61% reduction in 4 years with 105 total injections, thus requiring strict adherence. Inclisiran achieved a 44% reduction with 9 total injections. Both therapies are important to be available for health-care systems in order to be used as an adjunt to other treatments and better control LDL-c concentrations.

However, in order to have rigorous comparisons of efficacy between therapies, it would require a dedicated 3-arm trial with two active comparator arms and placebo.

Conclusion

Inclisiran is an adequate therapeutic option to reduce LDL-c levels over time in patients with high CV risk and elevated LDL-c. Inclisiran was well tolerated up to 4 years. This is the first long-term prospective study to assess repeat hepatic exposure to inclisiran.

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