NOVARTIS

ORION-8: Long-term assessment of the efficacy and safety of inclisiran in patients with high risk of cardiovascular events

Full abstract title: ORION-8: An open-label extension trial of ORION-3/9/10/11 to assess long-term efficacy and safety of twice-yearly inclisiran in patients with high cardiovascular risk and elevated LDL-C

Abstract authors: RS Wright, FJ Raal, W Koenig, U Landmesser, LA Leiter, GG Schwartz, A Lesogor, P Maheux, Z Talloczy, S Vikarunnessa, X Zang, KK Ray

Objectives of the study

To assess the efficacy and safety of inclisiran, in addition to stain therapy, when used over a long period of time to reduce the level of low-density lipoprotein cholesterol (LDL-C) in patients with high risk of experiencing a cardiovascular event, such as a stroke or heart attack[1].

What is LDL-C and its role in cardiovascular disease?

LDL-C, often called "bad cholesterol", is a lipid (fat), mainly produced by the liver, that circulates in the blood[2]. When the level of LDL-C in the blood is high, it can accumulate in the artery walls creating what is known as plaque[2].

Atherosclerotic cardiovascular disease (ASCVD) refers to a variety of diseases caused by the development of these plaques[3]. Because plaques build up silently, many people do not realize they are at risk of a cardiovascular event until a heart attack or stroke happens[3].

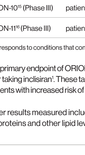
Arterial plaque formation

ATHEROSCLEROTIC PLAQUE

ASCVD is the most common form of cardiovascular disease (CVD), accounting for 85% of cardiovascular deaths[3]. Controlling LDL-C levels is therefore recommended to reduce the risk of ASCVD[4].

What is inclisiran?

Inclisiran showed consistent LDL-C reduction of **up to**



compared to placebo[†]

Inclisiran is the first and only siRNA (small interfering RNA) approved to help reduce high LDL-C levels when dietary changes and statins are not enough[5]. siRNA therapies are based on a natural cellular process that prevents the production of a specific protein in the body's cells[6].

The evidence that supported the approval of inclisiran in EU and in the US came from three Phase III clinical trials called ORION-9, -10 and -11, which compared the efficacy of inclisiran, in addition to statin therapy, with a placebo[7-9]. In these trials, inclisiran showed a reduction of LDL-C levels by up to 52% after 17 months, compared to placebo[7-9]. It was reported to be well-tolerated with a safety profile similar to placebo (mild to moderate injection site reactions were the most common adverse events with 8.2% with inclisiran vs. 1.8% with placebo)[7-9,10].

ORION-8 is part of **VictORION**, an innovative and robust clinical trial program that studies the efficacy and safety of inclisiran in reducing LDL-C in diverse patient populations. The program comprises **more than 30 studies** (from Phase I to Phase IV) and involves over 60,000 patients from more than 50 countries[11].

What did ORION-8 look at?

ORION-8 assessed the efficacy and safety of inclisiran when used long-term in patients with high risk of cardiovascular events (detailed in table below) and elevated LDL-C levels despite taking other medications[1,12].

ORION-8 followed patients from four previous trials – ORION-3, ORION-9, ORION-10 and ORION-11 – for up to three additional years[1,12].

Previous trial	Study population
ORION-3[13] (Phase II)	patients with ASCVD or at increased risk of ASCVD[†]
ORION-9[14] (Phase III)	patients with clinical or genetic evidence of heterozygous familial hypercholesterolemia (FH)
ORION-10[15] (Phase III)	patients with ASCVD
ORION-11[16] (Phase III)	patients with ASCVD or at increased risk of ASCVD[†]

[†] corresponds to conditions that confer a similar risk of an ASCVD event (e.g., diabetes)[17]

The primary endpoint of ORION-8 was to assess the **proportion of patients reaching their LDL-C targets** after taking inclisiran[1]. These targets were defined as **LDL-C <70mg/dL** (for ASCVD patients) **or <100mg/dL** (patients with increased risk of ASCVD, including FH) based on recommendations from medical societies[17,18].

Other results measured included the assessment of potential adverse events and the changes in LDL-C, lipoproteins and other lipid levels from the start of the trial to the end[1].

Study design and population

ORION-1: participants received up to 2 injections* over 1 year

ORION-3: participants received 7-9** injections* over 4 years

ORION-9, 10 & -11: participants received 4 injections* over 18 months

up to 3-year extension

ORION-8

3,274 participants enrolled receiving **up to 6**** additional injections* of inclisiran[12]

* Inclisiran is administered as a subcutaneous injection by a healthcare professional.

** The number of injections varies depending on the ORION-3 study groups (inclisiran vs placebo-switch to inclisiran)[12]

Patients enrolled in ORION-8 received 300mg of inclisiran sodium (284mg inclisiran) twice a year for up to 3 additional years after feeder studies[12]. 3,274 patients from 13 countries took part in the ORION-8 trial. The average age of participants at the beginning of the trial was 64.9 years[19].

At the start of ORION-8:

82.7% of the patients enrolled had ASCVD[12]

113.0 mg/dL was the mean baseline LDL-C (derived from the baseline of the initial feeder trials)[12]

What were the results?

78.4% of patients achieved their pre-specified LDL-C targets at the end of the study[1,12]

Approximately **90%** of patients achieved their global lipid target at any visit[12]

On average, LDL-C levels were reduced by approximately **50%** at the end of the study[12]

The overall mean exposure was **2.6 years**, and the total inclisiran exposure was **>8,000** patients-years[1,12]

[‡] LDL-C <70mg/dL (for ASCVD patients) or <100mg/dL (patients with increased risk of ASCVD, including FH)

Safety

The safety profile of inclisiran in ORION-8 was consistent with the previous studies[4,5,6,12]. Reactions at the injection site occurred in 5.9% of patients, compared with 8.2% in the inclisiran arm of the pooled analysis of ORION-9, -10, and -11 trials[6,12].

Why do the results matter?

With statins only, about 4 in 5 ASCVD patients do not reach recommended LDL-C levels[19].

Results from ORION-8 - the largest, long-term safety and efficacy follow-up trial with inclisiran conducted to date - show inclisiran could reduce LDL-C levels in the long-term while being well tolerated[12].

Glossary

Atherosclerosis cardiovascular disease (ASCVD): refers to a variety of diseases caused by the development of plaques in the arteries

Atherosclerotic plaque: lipid (mainly LDL-C) deposit in the arteries developing over time

Cardiovascular disease (CVD): disorder of the heart and the blood vessels

Familial hypercholesterolemia (FH): genetic disorder inducing high levels of LDL-C in the bloodstream

Heart attack (or myocardial infarction): occurs when the oxygen is not delivered to the heart, interrupting the function of the heart muscle

LDL-C (low-density lipoprotein cholesterol): a lipid (fat) mainly produced by the liver that can accumulate in the arteries over time and lead to ASCVD

Stroke: occurs when the blood flow to the brain is stopped therefore interrupting the oxygen and nutrients delivery to brain cells

Who sponsored this study?

Novartis Pharma AG, Basel, Switzerland sponsored both this study and the writing of this plain language summary.

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