# Clinical Efficacy and Cholesterol-Lowering Effects of Inclisiran

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## Abstract

Inclisiran, a drug developed by Novartis, is a recent medication designed to alleviate cardiovascular disease symptoms through improving low-density lipoprotein cholesterol levels. Mechanistically, inclisiran is a chemically synthesized small interfering RNA (siRNA) molecule targeting serine protease proprotein convertase subtilisin-kexin type 9 (PCSK9), resulting in degradation of the LDL receptor. Positive, large-scale clinical trials on the use of inclisiran demonstrate the drug's efficacy in reducing LDL cholesterol levels in patients afflicted with cardiovascular disease. Moreover, Novartis and the National Health Services (NHS) of the UK have very recently come to an agreement (September 1st, 2021) on the drug's utility, as the NHS has enabled inclisiran's use in more than 300,000 patients with a history of cardiovascular disease. However, despite the promising clinical trials on inclisiran as well as its use in the UK, the U.S. Food and Drug Administration (FDA) has yet to approve the drug as a treatment strategy for cardiovascular disease. This review will analyze and discuss the clinical efficacy of inclisiran based on the recent clinical evidence for its pharmacological use in the treatment of cardiovascular diseases.

Key words: Inclisiran, efficacy, cholesterol-lowering

## Introduction

For many years, cardiovascular disease (CVD) has been one of the leading causes of death globally, and in 2017 alone it accounted for 17.8 million deaths across the world (1). A significant risk factor for the development of CVD is hyperlipidemia or hypercholesterolemia, which is typically defined as an elevation in total fasting cholesterol levels (and possibly elevated triglycerides as well) (2). Importantly, lipids are insoluble in plasma and are instead transported via substances known as lipoproteins, which can then be measured to determine an individual's lipid status. Low density lipoprotein (LDL-C) is frequently measured, with values between 130-159mg/dL suggesting hyperlipidemia and values above 190mg/dL considered severely high and treatment (in the form of statins, lifestyle changes, etc.) is necessary (3). Thus, modifying cholesterol uptake or metabolism throughout the body may be one mechanism to improve hyperlipidemia and reduce the incidence of CVD.

Interestingly, a new class of drugs known as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have recently been developed to achieve this goal. Research in the early 2000's showed that mutations in the PCSK9 gene resulted in autosomal dominant hypercholesterolemia, and subsequent work demonstrated the protein is involved in the regulation and catabolism of the LDL-receptor (4,5). Specifically, PCSK9 degrades LDL-receptors resulting in diminished LDL-receptor recycling and LDL uptake. Due to this activity, pharmacological inhibition of PCSK9 has been proposed as a possible method to improve hyperlipidemia by preventing catabolism of the LDL-receptor and increasing cholesterol uptake. Recent clinical trials have illustrated PCSK9 inhibitors are successful in reducing LDL-cholesterol levels by as much as 60% and can significantly decrease the risk of developing adverse CVD events. One of these pharmacological agents is inclisiran, a long-acting, chemically synthesized siRNA covalently linked to a ligand with three N-acetylgalactosamine (GalNAc) residues. These residues bind directly to asialoglycoprotein receptors on hepatocytes, leading to inclisiran uptake (6). Importantly, hepatocyte-specific uptake of inclisiran has been reported in multiple studies, indicating the high specificity and efficacy of the drug (7,8). Once inclisiran enters the hepatocyte, the drug has specific cleavage activity of the PCSK9 mRNA, decreasing PCSK9 protein and, ultimately, preventing LDL-receptor breakdown. This review will discuss the recent clinical and scientific evidence (namely, the recent ORION trials) for inclisiran in the treatment of hyperlipidemia and CVD.

## Inclisiran in the Clinic

The first clinical investigation to assess inclisiran's effect on LDL cholesterol was funded by Alnylam Pharmaceuticals in 2014, and was also the first study to successfully show that an siRNA drug can be used to clinically validate an endpoint (9). The study was a randomized, single-blind, placebo-controlled phase I dose-escalation study on 32 healthy adults with normal serum LDL cholesterol level. 24 of the 32 participants were randomly selected to receive a single inclisiran dose (0.015mg/kg, 0.045mg/kg, 0.090mg/kg, 0.150mg/kg, 0.250mg/kg, 0.400mg/kg) and eight were given the placebo. Reports of adverse side effects were similar between the inclisiran-treated and placebo-treated groups (9). The most commonly stated side effects of the treatment and placebo groups was the presence of rashes around the injection site, and this adverse effect was particularly prevalent in the 0.400mg/kg, high-dose inclisiran group, although the data was insignificant. The researchers also discovered just a single-dose of inclisiran rapidly decreases PCSK9 protein in a dose-dependent manner, as plasma PCSK9 protein levels were reduced by 70% in the individuals given the 0.400mg/kg dose. This reduction in PCSK9 was accompanied by a 40% reduction in LDL-cholesterol from baseline values relative to placebo-treated control individuals as well, indicating the drug was not only effective at reducing PCSK9 protein, but that it has cholesterol-lowering capabilities as well. Overall, this was the first clinical investigation to show inclisiran displays a potent inhibitory effect on PCSK9 that can improve LDL-cholesterol levels, and provided a basis for further, more large-scale studies.

The ORION program consists of a sequence of clinical investigations aimed at testing the safety and efficacy of inclisiran use in hyperlipidemic or individuals with CVD. The ORION-2 investigation was a proof-of-concept study initially conducted to confirm the dose and regimen for subsequent phase-3 clinical trials using an open-label, single-arm treatment approach (10). All patients (n=5) of the study were previously diagnosed with homozygous familial hypercholesterolemia (HoFH), a genetic disorder characterized by elevated levels of LDL-cholesterol that typically results in premature atherosclerotic CVD, and the patients were also receiving statin or ezetimibe therapy as well. Patients were given a subcutaneous injection of inclisiran sodium (300mg) and monitored for 180 days. If PCSK9 levels were not suppressed by 70% or more, another dose was given either on day 90 or day 104. Interestingly, each participant receiving inclisiran experienced robust and long-term PCSK9 reductions. 3 of the patients showed a robust decline in their LDL-cholesterol levels as well, with levels declining as much as 37% from baseline at 180 days after treatment (10). One of the patients showed a notable reduction in PCSK9 protein but no reduction in LDL-cholesterol, but the authors reported this individual had a history of poor response to both of the currently marketed PCSK9-inhibiting monoclonal antibodies. The PCSK9 and LDL-cholesterol-lowering effects of inclisiran persisted at day 300 in 2 of the patients, indicating long-term efficacy after treatment with only 2 doses. One individual received only one inclisiran dose and PCSK9 levels remained suppressed for 300 days but LDL-cholesterol levels did not. Lastly, no adverse events or injection site reactions/rashes were reported by any of the study participants (10). This study, along with the aforementioned clinical trial funded by Alnylam Pharmaceuticals, provided the basis and framework for more thorough investigations which were conducted over the past couple of years.

The ORION-9, 10, and 11 clinical investigations are the 3 robust clinical trials analyzing the safety and efficacy of inclisiran for the treatment of **Homozygous familial hypercholesterolemia** (HoFH). Specifically, the ORION-9 study was a phase 3, double-blind trial on 480 adults with HoFH that were randomly assigned to either receive a subcutaneous injection of inclisiran sodium (300mg) or placebo on days 1, 90, 270, and 450 (11). The aim of the trial was to evaluate the effect of inclisiran treatment on LDL-cholesterol levels in HoFH-afflicted individuals. Median age of the patients was 56 years and 47% were male, and mean baseline levels of LDL-cholesterol amongst all participants was 153mg/dL. At day 510 of the study, LDL-cholesterol levels were measured and the inclisiran group showed a 39.7% reduction compared to an 8.2% increase in the placebo-treated individuals. Importantly, all genotypes of HoFH experienced robust reductions in LDL-cholesterol levels, and adverse events or serious side effects were similarly reported between both groups.

The ORION-10 trial was conducted in the United States on 1,561 adult participants with atherosclerotic CVD, elevated LDL-cholesterol levels (70mg/dL or higher), and who were receiving statin therapy (12). ORION-10 was a randomized, double-blind, placebo-controlled phase 3 clinical trial investigating the efficacy and safety of inclisiran use over an 18 month period. Overall, 781 patients with a mean age of ~65 years were treated with inclisiran and 780 were given the placebo, and 89.2% of these individuals were receiving high doses of statins. Mean LDL-cholesterol levels amongst all trial participants was 104.7 ± 38.3mg/dl (12). At day 510 of the study, the inclisiran-treated group demonstrated a robust 51.3% decline in LDL-cholesterol levels, compared to a 1.0% increase in the placebo-treated group, resulting in a 52.3% group difference. In terms of absolute change, inclisiran-treated participants experienced a 56.2mg/dL decline in LDL-cholesterol, while individuals given the placebo showed a modest 2.1mg/dL decline (12). This reduction in LDL-cholesterol at day 510 was concomitant with a 69.8% reduction in PCSK9 levels in the inclisiran group, compared to a 13.5% increase in the group given the placebo. Importantly, inclisiran-treated patients also displayed improvements in secondary end points at day 510 as well, including a reduction in total cholesterol, non-HDL cholesterol, and apolipoprotein B. Inclisiran-treated individuals also experienced a decrease in triglycerides and an increase in high-density lipoprotein (HDL) cholesterol (12). Concerning safety of inclisiran, 73.5% of individuals receiving the drug and 74.8% of participants given the placebo reported the presence of mild or moderate adverse events, the most common of which were similar between groups. Rash or injection-site specific side effects were more prevalent in the inclisiran group compared to those given the placebo. Finally, laboratory analysis of creatine kinase and C-reactive protein levels, liver and kidney function, and platelet counts were similar between groups.

In conjunction with the ORION-10 trials, the ORION-11 trial was a similarly run clinical trial conducted in Europe and South Africa comprised of adults with atherosclerosis CVD or atherosclerotic CVD-risk equivalent, such as type 2 diabetes, HoFH, or elevated risk of a CVD event over 10 years as determined by the Framingham Risk Score for CVD) (12). Eligibility for entry into the trial was similar to the ORION-10 trials except that patients with an elevated atherosclerotic CVD risk equivalent must have had LDL-cholesterol levels of 100mg/dL or higher, per the European Atherosclerosis Society (EAS) (12,13). Moreover, patients must have been receiving lipid-lowering therapies (statins, ezetimibe, etc.) for 30 days or more to be considered for entry into the study. The study design was similar to the ORION-10 trials as well – a total of 1,617 adult patients (mean age ~64.8) were randomized to inclisiran (284mg) or placebo treatments groups via subcutaneous injection, with injections taking place at days 1, 90, 270, and 450 (12). 810 participants were treated with inclisiran and 807 were given the placebo, and high-dose statin treatment was highly prevalent (94.7% of total study participants). After 510 days of treatment, the inclisiran-treated group showed a 45.8% decline in LDL-cholesterol concentration, compared to a 4.0% increase in participants given the placebo. The absolute change in LDL-cholesterol levels was a ~50.9mg/dL decline in the group given inclisiran, and a 1.0mg/dL increase in the placebo-treated group. Similar to the ORION-10 trial, the reduction in LDL-cholesterol in response to inclisiran treatment was accompanied by a 63.6% reduction in PCSK9 protein levels 510 days after the initial dose was given. Improvements in secondary end point factors were observed in the inclisiran-treated group as well (total cholesterol, apolipoprotein B, triglycerides, increased HDL-cholesterol, etc.). Adverse events and side effects of the ORION-11 trial were synonymous with ORION-10; no significant differences in severe or persistent side effects were identified between placebo and inclisiran-treated groups, but mild injection site-specific side effects were increased in the group treated with inclisiran (12). Together with the other ORION trials, the results of these studies indicate inclisiran is highly effective at reducing LDL-cholesterol levels in patients who are at risk of (or are already diagnosed with) CVD with minimal serious adverse complications.

## Concluding remarks

Overall, the very recent inclisiran clinical trials provide promising evidence for its utility as a cholesterol-lowering pharmaceutical drug in patients with HoFH or atherosclerotic cardiovascular disease. Based on data from over 2,500 patients across 3 clinical trials (ORION 9, 10, 11), minimal adverse effects were observed, suggesting the drug's safety. However, it remains to be seen if inclisiran can improve CVD as a whole – including hypertension, coronary artery disease, or stroke, or if the drug can be used as an alternative to statins when patients do not respond well to them. Furthermore, due to 'unresolved facility inspection-related conditions,' reported in 2020, the FDA has not approved inclisiran for LDL-cholesterol lowering use, but Novartis has conveyed they are actively working to resolve this issue (14).

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