

Leqvio[®] (inclisiran) Clinical Trials

Leqvio is the first and only FDA-approved small interfering RNA (siRNA) treatment that has demonstrated effective and sustained lowering of low-density lipoprotein cholesterol (LDL-C or "bad" cholesterol)¹. Leqvio is an injectable prescription medicine used along with diet and other lipid-lowering medicines in adults who need additional lowering of "bad" cholesterol and have known cardiovascular disease and/or heterozygous familial hypercholesterolemia (HeFH), an inherited condition that causes high levels of LDL-C. Ongoing clinical trials will determine if Leqvio can decrease problems related to high cholesterol, such as heart attacks or stroke¹.

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

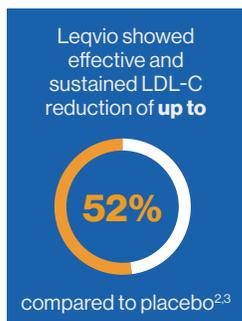


The ORION-9, -10 and -11 trials were multicenter, double-blind, randomized, placebo-controlled studies^{2,3}.

More than 3,400 patients were randomized to receive either placebo or Leqvio 284-mg treatment in addition to maximally tolerated statins with or without ezetimibe. Patients received an initial dose of Leqvio or placebo via subcutaneous injection, another dose at 3 months, then every 6 months thereafter^{2,3}.

A primary endpoint of percentage change (difference from placebo) in LDL-C from baseline to 17 months was met in all 3 trials^{2,3}.

STUDY RESULTS



ORION-9

LDL-C was reduced by 48% at 17 months vs placebo³.

- 482 patients with clinical or genetic evidence of HeFH
- 46 sites
- 8 countries (including the United States [US], Canada and Spain)

ORION-10

LDL-C was reduced by 52% at 17 months vs placebo².

- 1,561 patients with atherosclerotic cardiovascular disease (ASCVD)
- 145 sites
- Study was conducted in the US

ORION-11

LDL-C was reduced by 51% at 17 months vs placebo¹.

- 1,414 patients with ASCVD
- 70 sites
- 7 countries (including the United Kingdom and Germany)

SAFETY



Leqvio was reported to be well-tolerated, with a safety profile shown to be comparable to placebo. The most common side effects of Leqvio ($\geq 3\%$ of patients treated with Leqvio and occurring more frequently than placebo) were injection site reaction (including pain, redness and rash), arthralgia (joint pain), urinary tract infection, diarrhea, bronchitis, pain in legs or arms and dyspnea (shortness of breath)^{2,3}. Among the most common side effects, injection site reactions were the most frequent^{2,3}. These were generally mild, and none were severe or persistent^{2,3}.

ONGOING RESEARCH



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

- For every ~ 40 mg/dL (1 mmol/L) of LDL-C reduction, patients experience a 22% reduction in risk of major adverse CV event⁴
- This relationship is reflected in international clinical treatment guidelines as well⁵

The effect of Leqvio on CV morbidity and mortality has not been determined.

ORION-4

Novartis is currently conducting ORION-4, a randomized Phase III 5-year trial that aims to recruit 15,000 patients in the United Kingdom and the US to study the impact of Leqvio on CV outcomes, including patient mortality. The trial is expected to end in 2026.

VictORION-Inception

This trial will enroll in the US and assess the effect on LDL-C of implementing a care pathway with Leqvio compared to standard care in 384 randomized patients after a recent acute coronary syndrome event (~ 5 weeks) discharged on maximally tolerated statin therapy with LDL-C ≥ 70 mg/dL. The results will be compared to a Guideline Directed Medical Therapy (GDMT) control group. The trial is expected to end in 2023.

VictORION-Initiate

This trial will enroll in the US and assess the effect on LDL-C of a "Leqvio-first" ("high-intensity" statin plus Leqvio as the first non-statin therapy considered) implementation strategy compared to usual care in 444 randomized patients with ASCVD and an LDL-C ≥ 70 mg/dL, despite maximally tolerated statin therapy. The results will be compared to a GDMT control group. The trial is expected to end in 2023.

An overview of the clinical program*

The Leqvio clinical trial program (ORION-1 through ORION-12) includes 12 clinical trials in 20 countries, including the US, Canada, the United Kingdom, Germany, Spain, the Netherlands, Sweden and Denmark⁶.

12
trials

20
countries

more than
500
sites

more than
22,000[†]
patients

REFERENCES

1. LEQVIO prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021. 2. Ray KK, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382(16):1507-1519. 3. Raal FJ, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med*. 2020;382(16):1520-1530. 4. Baigent C, 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, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(11):111-188. 6. Data on File. Novartis Pharmaceuticals Corp; 2020.

*As of November 2021.

[†]Encompassing ORION-1 through ORION-12.



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