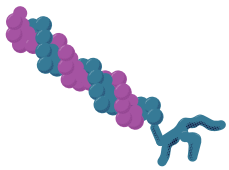
LEQVIO® – FROM DISCOVERY TO DEVELOPMENT

LEQVIO® (inclisiran) injection 284 mg/1.5 mL



LEQVIO is a small interfering RNA (siRNA) therapy that was studied in clinical trials to assess its efficacy and safety as a low-density lipoprotein cholesterol (LDL-C)-lowering therapy in certain patients with primary hyperlipidemia and atherosclerotic cardiovascular disease (ASCVD) or at increased risk of cardiovascular disease (CVD)[1*]

HOW WAS LEQVIO DEVELOPED?

siRNA DISCOVERY TO LEQVIO APPROVAL TIMELINE: OVER 30 YEARS OF RESEARCH

LEQVIO CLINICAL TRIALS IN PATIENTS WITH PRIMARY HYPERLIPIDEMIA AND ASCVD OR AT INCREASED RISK OF CVD[1*]

2016: Phase 2 clinical trial (ORION-1) began[7]
2017: Three Phase 3 clinical trials (ORION-9, 10 and -11) began[8-10]
2018: Phase 3 outcomes trial (ORION-4) began and is ongoing[11]
2019: Open-label Extension Trial (ORION-8) began[12]
2021: Phase 3 outcomes trial (VICTORION-2P) began and is ongoing[13]
2023: Phase 3 outcomes trial (VICTORION-1P) began and is ongoing[14]

1990 — First report of RNA interference (RNAi) in petunia flowers *(Petunia hybrida)*[2]

1995 — First report of RNA silencing (using single-stranded RNA) in a common animal model *(Caenorhabditis elegans)*[3]

1998 — First study to use double-stranded RNA for RNAi in *C. elegans*[4]

2006 — Nobel Prize in Physiology or Medicine awarded to Andrew Fire and Craig Mello for discovery of RNAi—suppression of gene activity by double-stranded RNA[4,6]

2016

2017

RNAi
- Cellular mechanism that regulates gene expression by preventing translation of specific messenger RNA (mRNA) into proteins[5]
- siRNAs bind to and inhibit target mRNA to prevent protein synthesis[5]
- Synthetic siRNAs are a class of drug that mimic the body's process of RNAi[6]

2018

2019

2020 — LEQVIO approved by the European Commission[15]

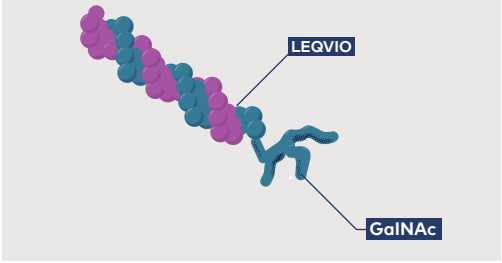
2021 — LEQVIO approved by the US Food and Drug Administration (FDA)[1]

2022

2023 — **FDA approved expanded indication that enables use of LEQVIO in patients with primary hyperlipidemia at increased risk of CVD[1*]**

FEATURES OF LEQVIO

Designed to target a specific mRNA sequence to prevent production of proprotein convertase subtilisin/kexin type 9 (PCSK9) in hepatocytes, which in turn increases recycling of LDL-C receptors at the cell surface to lower LDL-C levels[1]



LEQVIO reaches undetectable levels in circulation within 48 hours of administration[1]

Addition of N-acetylgalactosamine (GalNAc) targets LEQVIO specifically to the liver cell surface and reduces uptake into non-hepatic tissues[1]

*Factors that increase risk of CVD include heterozygous familial hypercholesterolemia, type 2 diabetes mellitus, or 10-year risk of ≥20%.[5]

INDICATION

LEQVIO injection is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).

IMPORTANT SAFETY INFORMATION

Adverse reactions in clinical trials (≥3% of patients treated with LEQVIO and more frequently than placebo) were injection site reaction, arthralgia, and bronchitis.

Please see accompanying LEQVIO full Prescribing Information.

1. Leqvio. Prescribing information. Novartis Pharmaceuticals Corp. 2. Napoli C et al. *Plant Cell*. 1990;2:279-289. 3. Guo S and Kemphues KJ. *Cell*. 1995;81(4):611-620. 4. Fire A et al. *Nature*. 1998;391(6669):806-811. 5. Ray KK et al. *N Engl J Med*. 2020;382(16):1507-1519 6. Khvorova A. *N Engl J Med*. 2017;376(1):4-7 7. ClinicalTrials.gov. NCT02597127. Accessed August 14, 2023. https://clinicaltrials.gov/ct2/show/NCT02597127. 8. ClinicalTrials.gov. NCT03397121. Accessed August 14, 2023. https://clinicaltrials.gov/ct2/show/NCT03397121 9. ClinicalTrials.gov. NCT03399370. Accessed August 14, 2023. https://clinicaltrials.gov/ct2/show/NCT03399370. 10. ClinicalTrials.gov. NCT03400800. Accessed August 14, 2023. https://clinicaltrials.gov/ct2/show/NCT03400800 11. ClinicalTrials.gov. NCT03705234. Accessed August 14, 2023. https://clinicaltrials.gov/ct2/show/NCT03705234 12. ClinicalTrials.gov. NCT03814187. Accessed August 14, 2023. https://www.clinicaltrials.gov/study/NCT03814187 13. ClinicalTrials.gov. NCT03814187. Accessed August 14, 2023. https://www.clinicaltrials.gov/ct2/show/NCT05030428 14. ClinicalTrials.gov. NCT05739383. Accessed August 14, 2023. https://www.clinicaltrials.gov/ct2/show/NCT05739383 15. www.novartis.com. LEQVIO® (inclisiran), a first-in-class siRNA to lower cholesterol with two doses a year. Accessed October 6, 2021. https://www.novartis.com/news/media-releases/novartis-receives-eu-approval-leqvio-inclisiran-first-class-sirna-lower-cholesterol-two-doses-year

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