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LEQVIO® inclisiran

ORION-8 CLINICAL FACT SHEET

LEQVIO®▼ (inclisiran) is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.[1]

A summary of: Wright RS, et al. Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial. *Cardiovasc Res* 2024;120(12):1400-1410

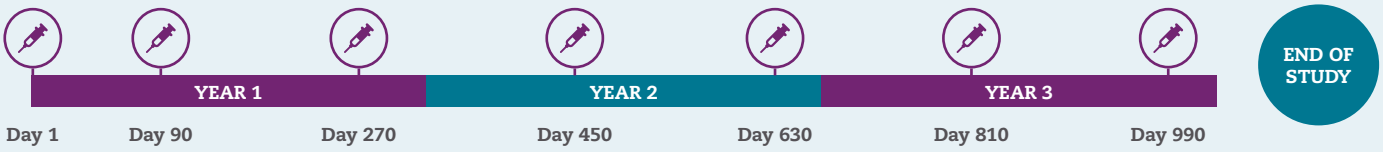
ORION-8 underscores the long-term efficacy and safety profiles of LEQVIO for your high-risk cardiovascular patients.

OBJECTIVE:[2]

ORION-8 was designed to **assess the long-term efficacy, safety and tolerability of LEQVIO** in patients who entered an open-label extension (ORION-8) **after completing either ORION-3, ORION-9, ORION-10 or ORION-11 trials**.[2]

TRIAL DESIGN & DOSING:[3]

An **international, open label, long term extension study (N=3,274, safety population)** in subjects with **ASCVD, ASCVD-risk equivalents** (e.g. diabetes and FH), or **HeFH or HoFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies** who have completed ORION-3 (Phase II trial), or one of ORION-9, ORION-10 or ORION-11 (Phase III trials). ORION-8 pre-specified lipid goals were <1.8 mmol/L (<70 mg/dL) in ASCVD patients and <2.6 mmol/L (<100 mg/dL) in ASCVD risk equivalents. Inclisiran (300 mg) was administered as a single subcutaneous injection on Day 1, 90, then every 180 days to Day 990. Patients who received blinded placebo in the feeder trials received blinded inclisiran and patients who received blinded inclisiran in the feeder trials received blinded placebo on Day 1. Subjects from ORION-3 study did not receive any injection on Day 1 until Day 90.



Adapted from Wright RS, et al. *Cardiovasc Res* 2024;120(12):1400-1410

KEY ENDPOINTS:[2]

Primary endpoint: Proportion of patients achieving pre-specified LDL-C goals at end of study & safety

Secondary endpoints: Percent change in LDL-C from baseline to end of study

KEY FINDINGS:

~80%
of patients reached LDL-C target

With **two maintenance doses a year**, and a baseline LDL-C of 2.92 mmol/L (-/+ 1.2) **almost 80% of patients with ASCVD on LEQVIO reached the <1.8 mmol/L LDL-C target**, in combination with maximum tolerated statin.[2] After an initial dose, LEQVIO is administered again at 3 months, followed by every 6 months.[1]

50%
average LDL-C reduction

In Phase III trials, LEQVIO showed **LDL-C reductions of about 50% from baseline on average seen as early as 90 days after initiation**, on top of a maximally tolerated dose of statin.*,[4] Results from the ORION-8 open label extension show **these results were sustained for up to ~3 years.**[2]

12,000
patient-years exposure

With over **12,000 patient-years exposure and >20,000 injections, the safety profile of LEQVIO remains consistent with no new safety signals identified**.[2] The only adverse reactions associated with LEQVIO were adverse reactions at the injection site (8.2%).†,[1]

In ORION-10, the baseline LDL-C levels were 2.70 ± 1.02 mmol/L for the LEQVIO group and 2.71 ± 0.96 mmol/L for the placebo group. LEQVIO achieved a 52% reduction in LDL-C relative to placebo from baseline (-51% reduction with LEQVIO vs. +1% with placebo, p<0.001). In ORION-11, baseline LDL-C levels were 2.77 ± 1.08 mmol/L for the LEQVIO group and 2.68 ± 0.94 mmol/L for the placebo group. LEQVIO demonstrated a 50% reduction in LDL-C relative to placebo from baseline (-46% reduction with LEQVIO vs. +4% with placebo, p<0.001).†,[1,4]

*Data from the multicentre, double-blind, randomised, placebo-controlled, 18-month ORION-10 (N=1,561) and ORION-11 (N=1,617) clinical trials evaluating adult patients on a maximally tolerated statin with ASCVD, and with ASCVD or risk equivalents, respectively. At Month 17, LEQVIO delivered placebo-corrected LDL-C reductions of 52%, as compared with baseline (–51% with LEQVIO vs +1% with placebo; 95% CI: –55.7 to –48.8; P<0.001) in ORION-10, and of 50%, as compared with baseline (–46% with LEQVIO vs +4% with placebo; 95% CI: –53.1 to –46.6; P<0.001) in ORION-11, with respective time adjusted LDL-C reductions of 54% (–51% with LEQVIO vs +3% with placebo; 95% CI: –56.2 to –51.3; P<0.001) and of 49% (–46% with LEQVIO vs +3% with placebo; 95% CI: –51.6 to –46.8; P<0.001) from baseline between Months 3 and 18 relative to placebo.[4]

†Data from the ORION-8 open label extension, a pooled cohort of 3,274 patients treated with LEQVIO with an assumed dosing frequency of two injections per year and an average treatment duration of 3.7 years.[2]

References: 1. LEQVIO® Summary of Product Characteristics; **2.** Wright RS, et al. *Cardiovasc Res* 2024;120(12):1400-1410; **3.** ClinicalTrials.gov. NCT03814187. Accessed August 08, 2023. https://clinicaltrials.gov/ct2/show/NCT03814187; **4.** Ray KK et al. *N Engl J Med* 2020;382(16):1507–1519

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