ORION-10 & ORION-11

LEQVIO® inclisiran

Two Phase III Trials of LEQVIO® (inclisiran) in Patients with Elevated LDL Cholesterol

A SUMMARY OF: RAY KK, WRIGHT RS, KALLEND D ET AL. N ENGL J MED 2020;382(16):1507-1519

The Phase III **ORION-10** (N=1,561) and **ORION-11** (N=1,617) clinical trials were designed to **assess the efficacy and safety profile of LEQVIO in adult patients with ASCVD, and ASCVD or ASCVD risk equivalents**, respectively, who had elevated LDL-C levels despite **receiving a maximally tolerated statin** with or without additional lipid-lowering therapy.[1]

Key findings:

- On top of a maximally tolerated statin, LEQVIO:[1,2]
  - Reduced LDL-C by 52% (95% CI: −55.7 to −48.8; P<0.0001) and 50% (95% CI: −53.1 to −46.6; P<0.0001) relative to placebo at Month 17, as compared with baseline, in ORION-10 and ORION-11, respectively
  - Delivered a time-adjusted LDL-C reduction of 54% (95% CI: −56.2 to −51.3; P<0.0001) and 49% (95% CI: −51.6 to −46.8; P<0.0001) from baseline between Months 3 and 18 relative to placebo in ORION-10 and ORION-11, respectively
    - ORION-10 baseline mean (±SD) LDL-C: LEQVIO—2.70±1.02 mmol/L; placebo—2.71±0.96 mmol/L
    - ORION-11 baseline mean (±SD) LDL-C: LEQVIO—2.77±1.08 mmol/L; placebo—2.68±0.94 mmol/L
- LEQVIO was generally well-tolerated, with a safety profile similar to placebo apart from injection-site reactions, which were more common in the LEQVIO group; these were graded as mild or moderate, with none being severe or persistent[1]

LEQVIO is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) 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.[2]

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report or alternatively email at medinfo.uk@novartis.com or call 01276 698370.

ASCVD=atherosclerotic cardiovascular disease; CI=confidence interval; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; SD=standard deviation

UK | January 2025 | FA-11297159-1

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Design:

Two randomised, double-blind, placebo-controlled, parallel-group, Phase III trials. The ORION-10 trial was conducted in the United States and included adults with ASCVD. ORION-11 was an international trial and included adults with ASCVD or ASCVD risk equivalents.[1]

Eligibility criteria included:[1,3]

- ≥18 years old
- History of ASCVD (CHD, CVD, or PAD) or, in ORION-11, also ASCVD-risk equivalents (type 2 diabetes, FH or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent)
- Serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) for patients with ASCVD or ≥2.6 mmol/L (≥100 mg/dL) for patients with ASCVD-risk equivalents, at screening
- Treatment with stable doses of background lipid-lowering therapies for at least 30 days before screening
- Patients on statins should be receiving a maximally tolerated dose:
  - Intolerance to any dose of any statin must have been documented in their medical history
  - Patients not receiving statin must have had documented evidence of intolerance to all doses of at least two different statins
- Patients receiving treatment with monoclonal antibodies directed toward PCSK9 within 90 days before screening were excluded

Baseline characteristics (ITT population)[1]

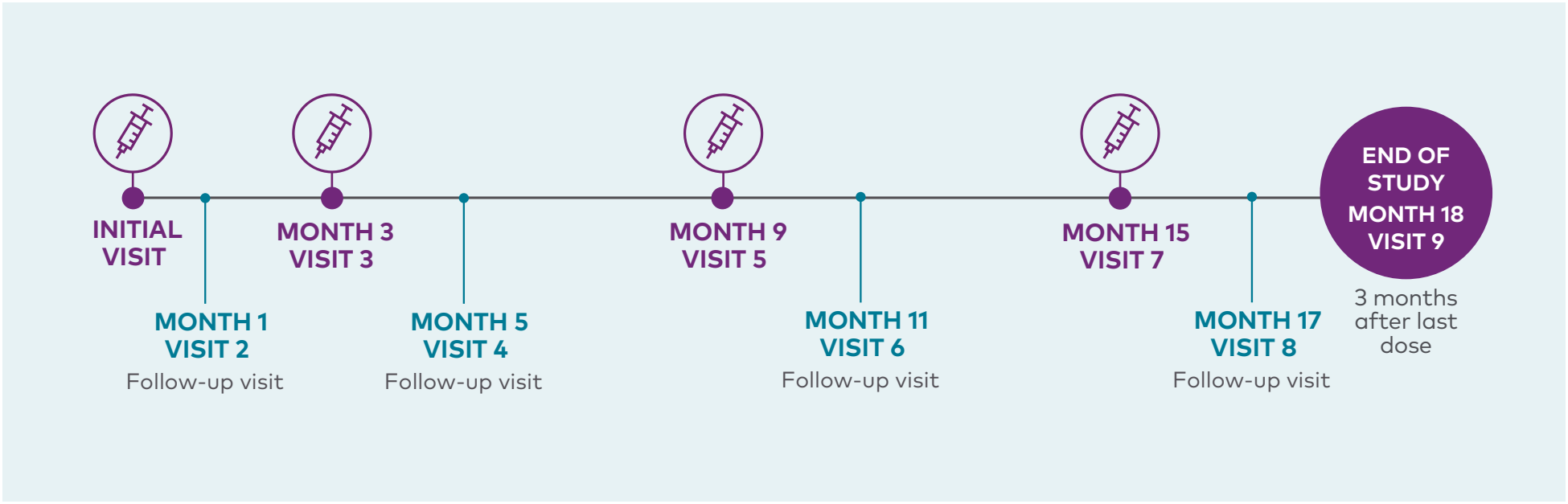
	ORION-10		ORION-11	
	LEQVIO (n=781)	Placebo (n=780)	LEQVIO (n=810)	Placebo (n=807)
Age (years), mean ± SD	66.4 ± 8.9	65.7 ± 8.9	64.8 ± 8.3	64.8 ± 8.7
Male sex, no. (%)	535 (68.5)	548 (70.3)	579 (71.5)	581 (72.0)
White race, no. (%)	653 (83.6)	685 (87.8)	791 (97.7)	796 (98.6)
Cardiovascular risk factors, no. (%)				
ASCVD	781 (100)	780 (100)	712 (87.9)	702 (87.0)
ASCVD risk equivalents	0	0	98 (12.1)	105 (13.0)
Current smoker	123 (15.7)	111 (14.2)	160 (19.8)	132 (16.4)
Hypertension	714 (91.4)	701 (89.9)	640 (79.0)	661 (81.9)
Diabetes	371 (47.5)	331 (42.4)	296 (36.5)	272 (33.7)
Heterozygous FH	8 (1.0)	12 (1.5)	14 (1.7)	14 (1.7)
Concomitant lipid-modifying therapy, no. (%)				
Statin	701 (89.8)	692 (88.7)	766 (94.6)	766 (94.9)
High-intensity statin	525 (67.2)	537 (68.8)	640 (79.0)	631 (78.2)
Ezetimibe	80 (10.2)	74 (9.5)	52 (6.3)	62 (7.7)
Lipid measures (mg/dL), mean ± SD				
LDL-C	104.5 ± 39.6	104.8 ± 37.0	107.2 ± 41.8	103.7 ± 36.4
Total cholesterol	180.6 ± 46.1	180.6 ± 43.6	187.3 ± 48.2	183.3 ± 42.8
Non-HDL-C	134.0 ± 44.5	134.7 ± 43.5	137.6 ± 46.9	133.9 ± 41.0
HDL-C	46.6 ± 14.3	45.9 ± 14.4	49.7 ± 15.5	49.3 ± 13.8
Apolipoprotein B	94.1 ± 25.6	94.6 ± 25.1	97.1 ± 28.0	95.1 ± 5.2

Adapted from Ray KK et al. N Engl J Med 2020.
Please note that this list is not exhaustive.

ASCVD=atherosclerotic cardiovascular disease; CHD=coronary heart disease; CVD=cerebrovascular disease; FH=familial hypercholesterolaemia; HDL-C=high-density lipoprotein cholesterol; ITT=intention-to-treat; LDL-C=low-density lipoprotein cholesterol; PAD=peripheral artery disease; PCSK9=proprotein convertase subtilisin/kexin type 9; SD=standard deviation

Dosing:

LEQVIO 284 mg or placebo was **administered subcutaneously by a healthcare professional** initially, again at Month 3, and then every 6 months over a period of 18 months. Additional follow-up visits took place on Months 1, 5, 11 and 17.[1,3]



Adverse events and clinical laboratory values were recorded at all visits through the end-of-trial visit (Month 18).[1]

Primary endpoints:[1]

- Placebo-corrected percentage change in LDL-C levels from baseline to Month 17
- Time-adjusted percentage change in LDL-C levels from baseline between Months 3 and 18

Key secondary endpoints:[1]

- Absolute change in LDL-C levels from baseline to Month 17
- Time-adjusted absolute change in LDL-C levels from baseline between Months 3 and 18
- Percentage change in levels of PCSK9, total cholesterol, apoliprotein B, and non-HDL-C from baseline to Month 17

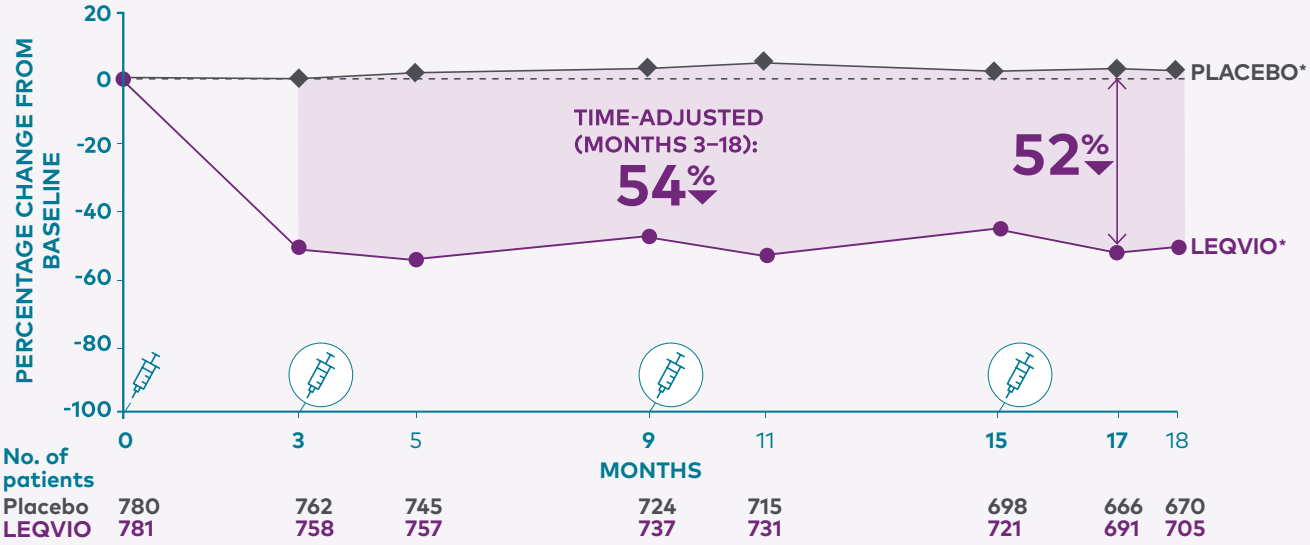
HDL-C =high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9

ORION-10 trial results

EFFICACY

Primary endpoints:[1,2]

- At Month 17, LEQVIO delivered **placebo-corrected LDL-C reductions** of 52.3%, as compared with baseline (95% CI: –55.7 to –48.8; P<0.0001)
- The **time-adjusted LDL-C reduction** was 53.8% from baseline between Months 3 and 18 relative to placebo (95% CI: –56.2 to –51.3; P<0.0001)



Adapted from Ray KK et al. N Engl J Med 2020.

*Reductions were achieved on top of a maximally tolerated statin and/or other lipid-lowering therapies.[1]

Key secondary endpoints:[1]

AS COMPARED WITH BASELINE:

- The **absolute change in LDL-C levels** at Month 17 was –1.40 mmol/L relative to placebo (95% CI: –1.48 to –1.32; P<0.001)
- The **percentage change in PCSK9 levels** at Month 17 was –83.3% relative to placebo (95% CI: –89.3 to –77.3; P<0.001)
  - ORION-10 baseline mean (±SD) PCSK9: LEQVIO—422.1± 176.9 µg/L; placebo—414.9±145.7 µg/L
- LEQVIO also resulted in improvement relative to placebo in other key secondary endpoints at Month 17, including lower **levels of total cholesterol, non-HDL-C and apolipoprotein B** (P<0.001)
- The **time-adjusted absolute change in LDL-C levels** between Months 3 and 18 was –1.38 mmol/L relative to placebo (95% CI: –1.44 to –1.31; P<0.001)

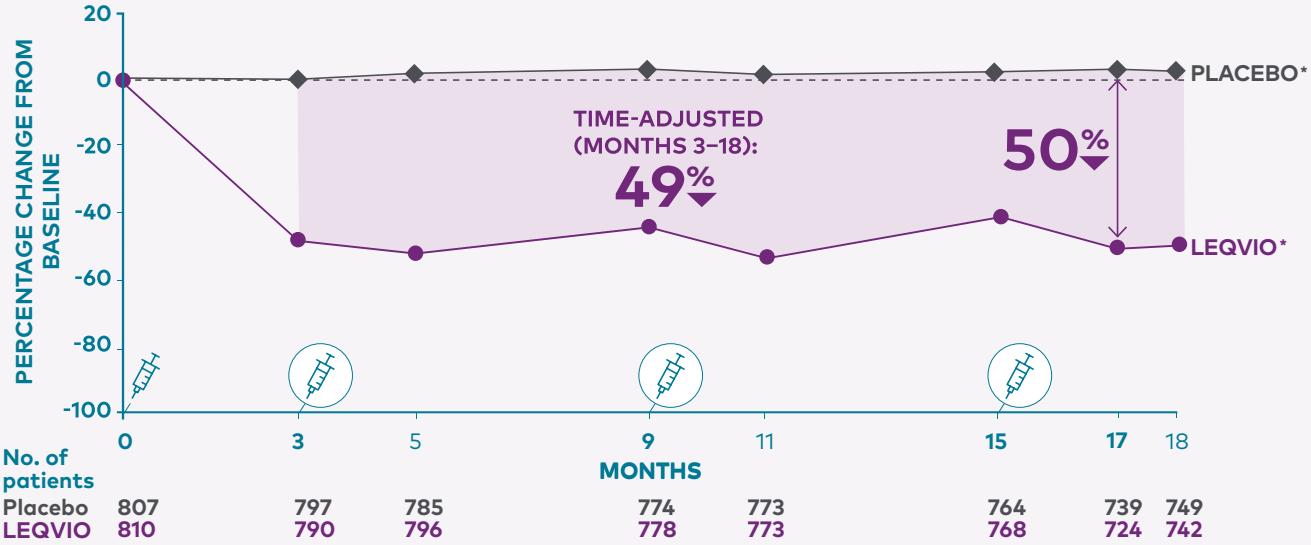
CI=confidence interval; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9

ORION-11 trial results

EFFICACY

Primary endpoints:[1,2]

- At Month 17, LEQVIO delivered **placebo-corrected LDL-C reductions** of 49.9%, as compared with baseline (95% CI: –53.1 to –46.6; P<0.0001)
- The **time-adjusted LDL-C reduction** was 49.2% from baseline between Months 3 and 18 relative to placebo (95% CI: –51.6 to –46.8; P<0.0001)



Adapted from Ray KK et al. N Engl J Med 2020.

*Reductions were achieved on top of a maximally tolerated statin and/or other lipid-lowering therapies.[1]

Key secondary endpoints:[1]

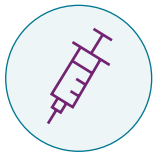
AS COMPARED WITH BASELINE:

- The **absolute change in LDL-C levels** at Month 17 was –1.34 mmol/L relative to placebo (95% CI: –1.42 to –1.26; P<0.001)
- The **percentage change in PCSK9 levels** at Month 17 was –79.3% relative to placebo (95% CI: –82.0 to –76.6; P<0.001)
  - ORION-11 baseline mean (±SD) PCSK9: LEQVIO—355.0± 98.9 µg/L; placebo—353.0± 97.4 µg/L
- LEQVIO also resulted in improvement relative to placebo in other key secondary endpoints at Month 17, including lower **levels of total cholesterol, non-HDL-C and apolipoprotein B** (P<0.001)
- The **time-adjusted absolute change in LDL-C levels** between Months 3 and 18 was –1.26 mmol/L relative to placebo (95% CI: –1.33 to –1.20; P<0.001)

CI=confidence interval; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9

SAFETY PROFILE

LEQVIO was generally well-tolerated in both trials, with a safety profile similar to placebo apart from injection-site reactions[1]



Injection-site adverse reactions were more frequent with LEQVIO than placebo, with between-group differences of 1.7% in ORION-10 and 4.2% in ORION-11; **the majority of these reactions were mild, with none being severe or persistent**[1]

Discontinuation rates due to adverse events were **balanced among both treatment groups**[1]

Laboratory results with respect to liver and kidney function, levels of creatine kinase and high-sensitivity C-reactive protein, and platelet count were also **similar in the LEQVIO and placebo groups in each trial**[1] and 4.2% in ORION-11; **the majority of these reactions were mild, with none being severe or persistent**[1]

LEQVIO was associated with adverse reactions at the injection site (8.2%)[2]

Adverse events (safety population)*[1]

	ORION-10			ORION-11		
	LEQVIO (n=781)	Placebo (n=778)	Risk ratio (95% CI)	LEQVIO (n=811)	Risk ratio (95% CI)	Placebo (n=804)
Adverse events, no. (%)						
≥1 Adverse event	574 (73.5)	582 (74.8)	1.0 (0.9–1.0)	671 (82.7)	655 (81.5)	1.0 (0.9–1.1)
≥1 Event leading to discontinuation	19 (2.4)	17 (2.2)	1.1 (0.6–2.1)	23 (2.8)	18 (2.2)	1.3 (0.7–2.3)
Serious adverse events, no. (%)						
≥1 Serious adverse event	175 (22.4)	205 (26.3)	0.9 (0.7–1.0)	181 (22.3)	181 (22.5)	1.0 (0.8–1.2)
Death	12 (1.5)	11 (1.4)	1.1 (0.5–2.4)	14 (1.7)	15 (1.9)	0.9 (0.4–1.9)
Death from cardiovascular causes	7 (0.9)	5 (0.6)	1.4 (0.4–4.4)	9 (1.1)	10 (1.2)	0.9 (0.4–2.2)
Cancer-related death	1 (0.1)	3 (0.4)	0.3 (0.0–3.2)	3 (0.4)	3 (0.4)	1.0 (0.2–4.9)
New, worsening, or recurrent cancer	26 (3.3)	26 (3.3)	1.0 (0.6–1.7)	16 (2.0)	20 (2.5)	0.8 (0.1–1.5)
Other cardiovascular adverse events, no. (%)						
Prespecified exploratory cardiovascular endpoint	58 (7.4)	79 (10.2)	0.7 (0.5–1.0)	63 (7.8)	83 (10.3)	0.8 (0.6–1.0)
Fatal or nonfatal myocardial infarction	20 (2.6)	18 (2.3)	1.1 (0.6–2.1)	10 (1.2)	22 (2.7)	0.5 (0.2–0.9)
Fatal or nonfatal stroke	11 (1.4)	7 (0.9)	1.6 (0.6–4.0)	2 (0.2)	8 (1.0)	0.2 (0.1–1.2)
Injection-site adverse events, no. (%)						
Any reaction	20 (2.6)	7 (0.9)	2.9 (1.2–6.7)	38 (4.7)	4 (0.5)	9.4 (3.4–26.3)
Frequent adverse events, no. (%)†						
Diabetes mellitus	120 (15.4)	108 (13.9)	1.1 (0.9–1.4)	88 (10.9)	94 (11.7)	0.9 (0.7–1.2)
Nasopharyngitis	—	—	—	91 (11.2)	90 (11.2)	1.0 (0.8–1.3)
Bronchitis	46 (5.9)	30 (3.9)	1.5 (1.0–2.4)	—	—	—
Dyspnoea	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)	—	—	—
Hypertension	42 (5.4)	42 (5.4)	1.0 (0.7–1.5)	53 (6.5)	54 (6.7)	1.0 (0.7–1.4)
Upper respiratory tract infection	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)	52 (6.4)	49 (6.1)	1.1 (0.7–1.5)
Arthralgia	—	—	—	47 (5.8)	32 (4.0)	1.5 (0.9–2.3)
Osteoarthritis	—	—	—	32 (3.9)	40 (5.0)	0.8 (0.5–1.2)
Back pain	39 (5.0)	39 (5.0)	1.0 (0.6–1.5)	—	—	—

Adapted from Ray KK et al. N Engl J Med 2020.
Please note that this table is not exhaustive.

* The safety population included all patients who received at least one dose of LEQVIO or placebo. Adverse events were recorded over the trial period of 18 months.[1]

†Shown are events occurring with a frequency of ≥5% in either the LEQVIO or placebo groups in each trial. Some events occurred with a frequency of <5% in one trial but not the other; a dash indicates that the frequency was <5% in that trial.[1]

CI=confidence interval

References
1. Ray KK et al. N Engl J Med 2020;382(16):1507-1519. **2.** Leqvio® Summary of Product Characteristics. **3.** Ray KK et al. N Engl J Med 2020;382(16):1507-1519 (supplementary appendix).

UK | January 2025 | FA-11297159-1

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