LEQVIO® inclisiran

LEQVIO® (inclisiran) for the Treatment of High LDL-C in Patients With Atherosclerotic Cardiovascular Disease or Atherosclerotic Cardiovascular Disease Risk Equivalent

ONE OF TWO PHASE III PIVOTAL TRIALS OF INCLISIRAN IN PATIENTS WITH ELEVATED LDL-C

Among adults with atherosclerotic cardiovascular disease (ASCVD), or an atherosclerotic cardiovascular disease risk equivalent (ASCVD-RE), those who received LEQVIO (inclisiran) with a maximally tolerated statin had significantly lower levels of LDL-C than those in the control group.[1,2] Patients were able to achieve approximately 50% reduction in LDL-C with inclisiran at Month 17.[1] Inclisiran has a twice-yearly dosing regimen and a well-tolerated safety profile.[1,2]

What was already known?

- Cardiovascular disease is the leading cause of death and disability worldwide[3]
- ASCVD and/or ASCVD-RE is a major driver of cardiovascular related events and mortality[4]
- ASCVD-RE patients have type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent[1]
- Many patients treated with statin-based, lipid lowering therapy are unable to consistently achieve and maintain their LDL-C target goals[5]
- Monoclonal antibodies have been shown to reduce LDL-C levels by more than 50% but require administration every 2 to 4 weeks[6]
- Inclisiran was developed and studied to address a substantial unmet medical need in patients with elevated LDL-C levels[7]

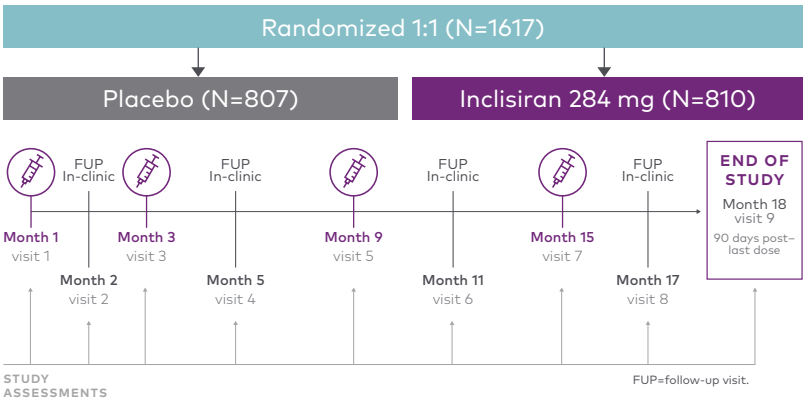
Why was ORION-11 conducted?

Previous studies showed that inclisiran, a small interfering RNA (siRNA), has the potential to substantially reduce LDL-C levels with a well-tolerated side effect profile and a twice-yearly dosing regimen. ORION-11 was conducted to evaluate the use of inclisiran in adults with ASCVD or ASCVD-RE with a maximally tolerated dose of statin (with or without ezetimibe).[7]

Study design

Design: A multicenter, placebo-controlled, double-blind study in 1617 patients randomized to receive either inclisiran 284 mg (300 mg of equivalent inclisiran sodium) or placebo on top of both groups taking a maximally tolerated dose of statin.[7]

Objective: Assess the effect of inclisiran on the efficacy and safety in patients with ASCVD, ASCVD-RE, and elevated LDL-C.[7]



Dosing frequency: Inclisiran 284 mg or placebo was administered initially, again at 3 months, and then every 6 months by a health care professional.[2]

Primary end points[1]:

- Percentage change from baseline in **LDL-C level** at Month 17
- Time-adjusted change from baseline in **LDL-C level** between Month 3 and Month 18

Selected secondary end points[1]:

- Mean percentage change in **total cholesterol** at Month 17
- Mean percentage change in **non–HDL-C** at Month 17

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Patients studied

1617 adult patients with ASCVD and ASCVD-RE in 72 centers in Europe and South Africa.[1]

Baseline characteristics	Placebo (N=807)	Inclisiran (N=810)
Age—yrs	64.8 ±8.7	64.8 ±8.3
Male sex—No. (%)	581 (72)	579 (71.5)
White race—No. (%)	796 (98.6)	791 (97.7)
Cardiovascular risk factors—No. (%)		
ASCVD	702 (87)	712 (87.9)
ASCVD-RE	105 (13)	98 (12.1)
Current smoker	132 (16.4)	160 (19.8)
Hypertension	661 (81.9)	640 (79)
Diabetes	272 (33.7)	296 (36.5)
HeFH	14 (1.7)	14 (1.7)
Concomitant lipid-modifying therapy—No. (%)*		
Statin	766 (94.9)	766 (94.6)
High-intensity statin*	631 (78.2)	640 (79)
Ezetimibe	62 (7.7)	52 (6.3)
Baseline cholesterol—mg/dL		
Low-density lipoprotein	103.7 ±36.4	107.2 ±41.8

*Patients on low-intensity statins include those patients taking low-dose statins using an alternate regimen (ie, every other day or for a specified number of times per week). Patients on high-intensity statin therapy were taking at least 20 mg of rosuvastatin, 40 mg of atorvastatin, 40 mg of simvastatin, or the equivalent per day.[1]

Inclusion criteria[7]:

- ≥18 years of age
- History of ASCVD (CHD, CVD, or PAD)
- Patients on statins should have been taking a maximally tolerated dose with or without ezetimibe (participants on statin and/or ezetimibe should have been on a stable dose for at least 30 days before screening with no planned change in medication/dose during the study)
- Statin-intolerant patients needed documentation of unacceptable adverse events to more than one statin
- Serum LDL-C ≥1.8 millimoles (mmol/liter) or ≥70 mg/dL at screening and fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening
- Patients on statins should have been receiving a maximally tolerated dose with or without ezetimibe

What are the results and why are they significant?

The ORION-11 study evaluated twice-yearly dosing in inclisiran patients with ASCVD or ASCVD-RE with maximally tolerated statin therapy. The data collected from the study show how the novel approach of inclisiran reduced LDL-C levels in patients with ASCVD or ASCVD-RE.

Efficacy

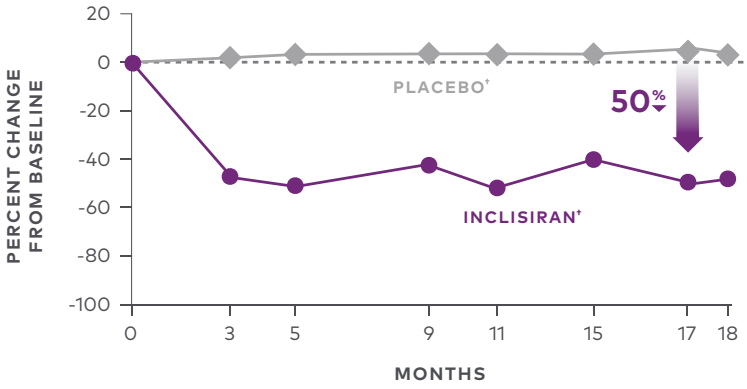
Primary end points[1]:

- Percentage change in **LDL-C level** at Month 17 compared with placebo:
  - Between-group difference, inclisiran vs placebo: -49.9% (95% confidence interval [CI], -53.1 to -46.6; *P*<0.001)
- Time-adjusted change in **LDL-C level after Month 3 and up to Month 18** from baseline as compared with placebo:
  - Between-group difference, inclisiran vs placebo: -49.2% (95% CI, -51.6 to -46.8; *P*<0.001)

Selected secondary end points[2]:

- Mean percentage change in **total cholesterol level** at Month 17:
  - Placebo-adjusted difference: -30%
- Mean percentage change in **non–HDL-C level** at Month 17:
  - Placebo-adjusted difference: -43%

Reduction in LDL-C with inclisiran vs placebo during the 18-month trial period—on top of a maximally tolerated statin dose[1]



NO. OF PATIENTS†								
PLACEBO	807	797	785	774	773	764	739	749
INCLISIRAN	810	790	796	778	773	768	724	742

†Patients in both groups were taking maximally tolerated statin therapy.

Safety

In the ORION-11 trial, 2 patients who were assigned to the placebo group did not receive placebo, and 1 patient who was assigned to placebo was given a dose of inclisiran in error and is included in the inclisiran group for safety reporting; therefore, the safety population of the trial comprises 811 patients exposed to inclisiran and 804 patients exposed to placebo.

Adverse events that occurred during the trial period, regardless of causality, were reported in 671 of 811 patients (82.7%) receiving inclisiran and 655 of 804 patients (81.5%) receiving placebo.

The majority of events in the trial were reported to be mild or moderate, with the most common adverse events occurring with similar frequency in the inclisiran and placebo groups. Injection site adverse events were more frequent with inclisiran than with placebo, with a between-group difference of 4.2 percentage points in the ORION-11 trial.[1]

Inclisiran was undetectable in patients' plasma 48 hours after administration.[8]

Implications for clinical practice

This study shows that among patients with ASCVD or ASCVD-RE, inclisiran can be used for significant reduction in LDL-C.[1] This was well tolerated with no signs of liver, muscle, or kidney toxicity. The use of a small interfering RNA (siRNA) molecule is a novel approach for clinical use in management of LDL-C.[1]

- Inclisiran significantly reduced the LDL-C level from baseline to Month 17 vs placebo[2]
- Inclisiran showed improvement to overall lipid levels at Month 17[2]
- Inclisiran also provided sustained LDL-C reduction from Month 3 to Month 18[2]
- The results for the percentage change in LDL-C levels at Month 17 were consistent across subgroups with no dosing adjustments required, including patients with renal impairment[1,9]
- Discontinuation due to adverse events was similar with patients taking inclisiran vs placebo in the 3 Phase III clinical trials[7]

REFERENCES

1. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387 **2.** Leqvio. Summary of product characteristics. Novartis Pharma AG; 2020. **3.** Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016— 40 for 195 countries and territories. *Lancet*. 2018;392(10159):2052-2090. doi:10.1016/S0140-6736(18)31694-5 **4.** Cherepanov D, Bentley TGK, Hsiao W, et al. Real-world cardiovascular disease burden in patients with atherosclerotic cardiovascular disease: a comprehensive systematic literature review. *Curr Med Res Opin*. 2018;34(3):459-473. doi:10.1080/03007995.2017.1401529 **5.** Jones PH, Nair R, Thakker KM. Prevalence of dyslipidemia and lipid goal attainment in statin-treated subjects from 3 data sources: a retrospective analysis. *J Am Heart Assoc*. 2012;1(6):1-10. doi:10.1161/JAHA.112.001800 **6.** Raal FJ, Kallend D, Ray KK, et al; ORION-9 Investigators. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med*. 2020;382(16):1520-1530. doi:10.1056/NEJMoa1913805 **7.** Data on file. ORION-11 (MDCO-PCS-17-08) Clinical Study Report. The Medicines Company; 2019. **8.** Protocol for: Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387 **9.** Data on file. Core Data Sheet (Version 1.0). Novartis Pharma AG; 2020.

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Felleskatalogtekst

▼**LEQVIO®** «Novartis»
C

Lipidmodifiserende middel. **ATC-nr.: C10A X16**

INJEKSJONSVÆSKE, oppløsning i ferdigfylt sprøyte 284 mg: Hver ferdigfylte sprøyte (1,5 ml) inneh.: Inklisirannatrium tilsv. inklisiran 284 mg, natriumhydroksid/konsentrert fosforsyre (til pH-justering), vann til injeksjonsvæsker.1

Indikasjoner: Voksne med primær hyperkolesterolemi (heterozygot familiær og ikke-familiær) eller blandet dyslipidemi, som tilleggsbehandling til diett: I kombinasjon med et statin eller statin sammen med annen lipidsenkende behandling hos pasienter som ikke oppnår LDL-C-mål med høyeste tolererte dose av et statin, eller alene eller i kombinasjon med annen lipidsenkende behandling ved statinintoleranse, eller der et statin er kontraindisert.

Dosering: Voksne inkl. eldre ≥65 år: 284 mg (1 ferdigfylt sprøyte) som 1 s.c. injeksjon. Neste dose gis etter 3 måneder, og deretter hver 6. måned. Overgang fra behandling med PCSK9-hemmende monoklonale antistoffer: Inklisiran kan gis umiddelbart etter siste dose med PCSK9-hemmende monoklonalt antistoff. For å opprettholde LDL-C-reduksjon anbefales det at inklisiran gis <2 uker etter siste dose med PCSK9-hemmende antistoff. Glemt dose: Ved <3 måneder siden forrige dose skulle vært tatt, skal inklisiran gis og dosering fortsettes iht. opprinnelig plan. Ved >3 måneder siden forrige dose skulle vært tatt, skal ny doseringsplan startes. Spesielle pasientgrupper: Nedsatt leverfunksjon: Ingen dosejustering nødvendig ved lett/moderat nedsatt leverfunksjon. Bør brukes med forsiktighet ved alvorlig nedsatt leverfunksjon, pga. manglende data. Nedsatt nyrefunksjon: Ingen dosejustering nødvendig ved lett, moderat eller alvorlig nedsatt nyrefunksjon eller terminal nyresvikt. Bør brukes med forsiktighet ved alvorlig nedsatt nyrefunksjon, pga. begrenset erfaring. Barn og ungdom < 18 år: Sikkerhet og effekt ikke fastslått. Ingen data. Tilberedning/Håndtering: Kun til engangsbruk. Skal undersøkes visuelt før administrering. Oppløsningen skal være klar, fargeløs til lysegul og praktisk talt partikkelfri. Skal ikke brukes ved synlige partikler. Skal ikke blandes med andre legemidler. Administrering: Injiseres s.c. i abdomen, ev. overarm eller lår. Bør ikke injiseres i hudområder med aktiv hudsykdom eller skade som solbrenthet, utslett, inflammasjon eller hudinfeksjoner. Administreres av helsepersonell.

Kontraindikasjoner: Overfølsomhet for innholdsstoffene.

Forsiktighetsregler: Effekten av hemodialyse på farmakokinetikken er ikke undersøkt. Pga. renal eliminasjon bør hemodialyse ikke utføres i minst 72 timer etter dosering. Hjelpestoffer: Inneholder <1 mmol (23 mg) natrium pr. dose, og er så godt som natriumfritt. Bilkjøring og bruk av maskiner: Ingen eller ubetydelig påvirkning på evnen til å kjøre bil eller bruke maskiner.

Interaksjoner: For utfyllende informasjon om relevante interaksjoner, bruk interaksjonsanalyse.
Inklisiran er ikke substrat, hemmer eller induktor for vanlige legemiddeltransportører. Forventes ikke å være CYP450-substrat, og er ikke CYP450-hemmer/-induktor. Klinisk signifikante legemiddelinteraksjoner forventes derfor ikke. Det forventes ikke klinisk betydningsfulle interaksjoner med atorvastatin, rosuvastatin eller andre statiner ut ifra begrensede data.

Graviditet, amming og fertilitet: Graviditet: Ingen/begrenset mengde data. Dyrestudier indikerer ingen direkte eller indirekte skadelige effekter mtp. reproduksjonstoksisitet. Det er anbefalt å unngå bruk under graviditet. Amming: Utskillelse i morsmelk er ukjent. Dyrestudier har vist utskillelse i melk. En risiko for nyfødte/spedbarn som ammes kan ikke utelukkes. Det må tas en beslutning om amming skal opphøre eller behandling avstås fra, basert på nytte-/risikovurdering. Fertilitet: Ingen data. Dyrestudier viser ingen effekt på fertilitet.

Bivirkninger: Vanlige (≥1/100 til <1/10): Generelle: Bivirkninger på injeksjonsstedet1.
1Hyppigst rapportert er reaksjon, smerte, erytem eller utslett på injeksjonsstedet.

Overdosering/Forgiftning: Symptomer: Det er ikke sett klinisk relevante bivirkninger hos friske etter 3 × terapeutisk dose. Behandling: Symptomatisk og støttetiltak hvis nødvendig.

Egenskaper: Virkningsmekanisme: Inklisiran er en dobbelttrådet, liten interferende ribonukleinsyre (siRNA) konjugert på sense-tråden med triantennært N-acetylgalaktosamin for å fasilitere opptak via hepatocytter. I hepatocyttene utnytter inklisiran RNA-interferensmekanismen og gir katalytisk nedbrytning av mRNA for proproteinkonvertasesubtilisin/kexin-type 9. Dette øker LDL-C-reseptorresirkulering og -uttrykk på celleoverflaten av hepatocytter, noe som øker opptaket av LDL-C og gir redusert LDL-C-nivå i sirkulasjonen. Absorpsjon: Tmax ca. 4 timer. Gjennomsnittlig Cmax er 509 ng/ml. Konsentrasjonen falt til ikke-detekterbart nivå innen 48 timer etter dosering. Selektiv målstyring til hepatocytter, hvor det inkorporeres i RNA-indusert slukningskompleks (RISC), gir en langvarig effekt utover det som forventes fra t1/2. Proteinbinding: 87% in vitro. Fordeling: Vd ca. 500 liter. Tas i høy grad opp i leveren. Halveringstid: 9 timer. Metabolisme: Primært av nukleaser til kortere inaktive nukleotider. Utskillelse: 16% via nyrene.

Oppbevaring og holdbarhet: Skal ikke fryses.

Pakninger og priser: 1 stk. (ferdigfylt sprøyte) kr. 31461.20.

Sist endret: 30.04.2021
Basert på SPC godkjent av SLV/EMA: 04.08.2021

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