swissmedic

Date: 20 July 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

LEQVIO

International non-proprietary name:	inclisiran
Pharmaceutical form:	Solution for injection in pre-filled syringe
Dosage strength(s):	Each pre-filled syringe contains 1.5 ml of solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium)
Route(s) of administration:	Subcutaneous injection
Marketing authorisation holder:	Novartis Pharma Schweiz AG
Marketing authorisation no.:	67836
Decision and decision date:	extension of therapeutic indication approved on 02.07.2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Hypercholesterolaemia and mixed dyslipidaemia
Leqvio is indicated in adults with hypercholesterolaemia [including heterozygous familial hypercholesterolaemia] or mixed dyslipidaemia as an adjunct to diet, and in paediatric patients 12 years of age and older with heterozygous familial hypercholesterolaemia (HeFH)

- In combination with a maximally tolerated statin dose with or without other lipid-lowering therapies in patients requiring an additional reduction in low-density lipoprotein cholesterol (LDL-C), or
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom

Homozygous familial hypercholesterolaemia
Leqvio is indicated as adjunct therapy to other LDL-C-lowering therapies for the treatment of paediatric patients between 12 and no more than 18 years old with homozygous familial hypercholesterolemia (HoFH).

2.2.2 Approved indication

Hypercholesterolaemia and mixed dyslipidaemia
Leqvio is indicated in adults with hypercholesterolaemia [including heterozygous familial hypercholesterolaemia] or mixed dyslipidaemia as an adjunct to diet, and in paediatric patients 12 years of age and older with heterozygous familial hypercholesterolaemia (HeFH)

- In combination with a maximally tolerated statin dose with or without other lipid-lowering therapies in patients requiring an additional reduction in low-density lipoprotein cholesterol (LDL-C), or
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom

Homozygous familial hypercholesterolaemia
Leqvio is indicated as adjunct therapy to other LDL-C-lowering therapies for the treatment of paediatric patients between 12 and no more than 18 years old with homozygous familial hypercholesterolemia (HoFH).

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	14 November 2025
Formal control completed	24 November 2025
List of Questions (LoQ)	23 February 2026
Response to LoQ	9 April 2026
Preliminary decision	18 June 2026
Response to preliminary decision	24 June 2026
Final decision	2 July 2026
Decision	approval

3 Medical context

Familial hypercholesterolaemia (FH) is a genetic disorder characterised by lifelong elevated LDL-C levels and a markedly increased risk of premature atherosclerotic cardiovascular disease (ASCVD). FH results from pathogenic variants affecting LDL receptor-mediated LDL-C clearance and occurs as heterozygous (HeFH; ~1:250–300) or homozygous (HoFH; ~1:250,000–360,000) disease.

Early and sustained LDL-C reduction is essential, as cumulative LDL-C exposure drives atherosclerotic burden. Despite available therapies, including statins, ezetimibe, PCSK9 inhibitors and, for HoFH, ANGPTL3 inhibition, many patients — particularly adolescents — do not achieve recommended LDL-C targets. Treatment adherence is often challenging during adolescence, highlighting the need for effective therapies.

HeFH is associated with accelerated atherosclerosis that begins in childhood, although clinical manifestations usually occur later in life. Long-term data support initiation of lipid-lowering therapy in childhood to reduce future cardiovascular risk.

HoFH is a severe and rare form of FH characterised by extremely elevated LDL-C levels, early-onset ASCVD, and significant morbidity and mortality if inadequately treated. Management remains challenging despite multiple treatment options, including LDL apheresis, PCSK9 inhibitors, lomitapide and evinacumab.

Overall, a significant unmet medical need remains for adolescents with HeFH or HoFH who require early, intensive and lifelong LDL-C lowering. Additional effective treatment options, particularly those reducing the burden of frequent administration, could provide meaningful clinical benefit.

4 Clinical aspects

4.1 Clinical pharmacology

This section outlines the clinical pharmacology of inclisiran in the ORION-16 and ORION-13 studies, which support its use in adolescents aged 12 to 17 years with HeFH or HoFH. It should be noted that the adolescents received the same dose and dosing regimen as that approved for adults: 300 mg of inclisiran sodium was administered subcutaneously initially, then at 90 days (three months) and subsequently every 180 days (six months), and the formulation was the same.

Pharmacokinetics in adolescents with HeFH (ORION-16)
Following a single s.c. administration of inclisiran sodium 300 mg, inclisiran concentrations peaked at 4 hours post injection (mean 905; range: 225 to 3010 ng/mL) in ORION-16. At 24 hours post-dose, inclisiran concentrations had decreased to substantially lower levels (mean 65.7 ng/mL; range 0 to 143 ng/mL). These ranges substantially overlap with the inclisiran plasma concentrations at 4 hours (range: 371 to 1071 ng/mL, n=4) and 24 hours (12 to 206 ng/mL, n=4) in adults who had received inclisiran sodium 300 mg and taken a statin.
In the adolescent studies, sparse PK sampling was conducted at pre-dose (prior to injection), 4 hours and 24 hours after the first dose of inclisiran on Day 1. Inclisiran concentrations at these timepoints were compared to those measured in adults at the same timepoints to assess any differences. Additionally, due to sparse PK sampling in ORION-16 and ORION-13, a population PK model was established using data from both adults and adolescents to estimate individual PK parameters for adolescents.

Pharmacokinetics in adolescents with HeFH (ORION-13)
Following a single s.c. administration of inclisiran sodium 300 mg, inclisiran concentrations peaked at 4 hours post injection (mean 1118.2 ng/mL; range: 461 to 1930 ng/mL) in ORION-13. At 24 hours post-dose, inclisiran concentrations had decreased to substantially lower levels (mean 56.9 ng/mL; range 0 to 141 ng/mL). These ranges substantially overlap with the inclisiran plasma concentrations at 4 hours (range: 371 to 1071 ng/mL, n=4) and 24 hours (12 to 206 ng/mL, n=4) in adults who had received inclisiran sodium 300 mg and taking a statin.

4.2 Dose finding and dose recommendation

The approved dose regimen for adults is inclisiran sodium 300 mg s.c. initially, at month 3, and every 6 months thereafter. Based on nonclinical findings, adult clinical data (Phase I–III), and PD modelling, the same dose and regimen were selected for adolescents in ORION-13 and ORION-16.

Preclinical studies identified no paediatric-specific safety concerns. In adults, a 300 mg dose achieved maximal LDL-C and PCSK9 reduction, with no clinically meaningful additional benefit at higher doses. Phase III studies demonstrated robust and sustained LDL-C lowering, good tolerability, and a safety profile comparable to placebo except for increased injection site reactions. No dose adjustments were required for patients with renal or hepatic impairment, and doses up to 900 mg were well tolerated. Inclisiran is rapidly cleared from plasma, distributes primarily to the liver, and is partly eliminated via the kidneys. As hepatic and renal maturation is completed well before adolescence, and no increased safety risks were observed in adults with hepatic or renal impairment, no additional paediatric safety concerns were anticipated.

A dissociation between PK and PD has been demonstrated, with LDL-C-lowering effects persisting for more than 6 months despite rapid plasma clearance, supporting the 6-monthly dosing interval. As PK/PD relationships could not be used directly for dose selection, extrapolation from adult efficacy and safety data was considered appropriate. Given that inclisiran metabolism and elimination are expected to be similar in adolescents and adults, the 300 mg dose regimen used in adults was selected for the adolescent studies, in line with the EU PIP.

4.3 Efficacy

Pivotal studies
Efficacy, safety, and tolerability of inclisiran in adolescents were studied in two randomised, multicentre, international, Phase III studies in participants aged 12 to <18 years with HeFH (ORION-16) and HoFH (ORION-13), respectively.

Given the small sample size of the ORION-13 study (N=13), the safety data in adolescents with HoFH have to be seen in the context of the safety data of the parallel study in adolescents with HeFH (ORION-16; N=141) as well as the already established safety profile of inclisiran in adults with hypercholesterolaemia. Specifically, the safety data generated from the adult study in HoFH, ORION-5 (N=56), are considered relevant and are included as supportive safety data.

The primary objective of ORION-16 was to demonstrate superiority of inclisiran compared to placebo in reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HeFH and elevated LDL-C.

The primary objective of ORION-13 was to evaluate the effect of inclisiran compared to placebo on reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HoFH and elevated LDL-C. The study did not include formal hypothesis testing due to the small sample size (which was based on feasibility due to HoFH being a very rare condition).

While it is useful to present the data from the ORION-16 and ORION-13 studies together, given that they are both FH studies in adolescents with very similar study designs, considering that HeFH and HoFH are different disease manifestations in severity, prevalence and treatment modalities, as well as taking into account the very small sample size of ORION-13, efficacy data of ORION-16 and ORION-13 were not pooled, and the results of both studies are presented separately.

<u>HeFH (ORION-16)</u>
A total of 141 participants were randomised, 93 in the inclisiran group and 48 in the placebo group. Almost all participants completed Study Part 1 and received the Part 1 study treatment (98.6% (139/141) overall, 97.8% (91/93) in the inclisiran group and 100% (48/48) in the placebo group). The two study discontinuations were due to subject/guardian decision and physician decision.

Primary efficacy endpoint
Inclisiran was superior to placebo in lowering LDL-C in adolescents with HeFH. The least square (LS) mean percent change (95% CI) in LDL-C from baseline to Day 330 was -27.14% (-32.04, -22.24) in the inclisiran group and +1.40% (-3.97, 6.78) in the placebo group, with a between-group difference of –28.54% (95% CI –35.81, -21.27; 1-sided p<0.0001).
Sensitivity analyses results assessing the robustness of the primary efficacy analysis were consistent with the primary analysis independent of the sensitivity analysis used.

Key secondary efficacy endpoints
Relevant improvements consistent with the primary efficacy endpoint were seen for time-adjusted percent change in LDL-C. The LS mean change was –26.04% in the inclisiran group and +3.26% in the placebo group, with a between-group difference of –29.30% (95% CI –36.24, –22.36; p<0.0001).
Relevant improvements consistent with the primary efficacy endpoint were also seen for the other key secondary endpoints of absolute change in LDL-C and percent change in apolipoprotein B (ApoB), non-HDL-C and total cholesterol. The LS mean between-group differences at Day 330 were -49.99 mg/dL, –25.7%, –26.8% and –19.2%, respectively (all p-values <0.0001).
For lipoprotein (a) (Lp(a)), using the primary analysis method (ANCOVA), the p-value for the observed small reduction (LS mean between group difference -6.2%) was 0.1419. The supplementary analysis, using log transformation to account for the skewed distribution of this parameter, showed a ratio of

geometric means inclisiran/placebo (95% CI) of 0.90 (0.80,1.00) in favour of inclisiran, with a p-value of 0.0212.

Other secondary efficacy results
Inclisiran reduced LDL-C rapidly, with effects evident by Day 90, maximal at Day 150, and maintained through Day 330. Consistent improvements were observed for ApoB, non-HDL-C, total cholesterol and Lp(a). PCSK9 levels were markedly reduced (−72.9% vs +4.8% with placebo; p<0.0001). Modest increases in HDL-C and ApoA1 were observed, whereas triglycerides and VLDL-C were unchanged. LDL-C reductions were sustained through Day 720 in participants continuously treated with inclisiran and were reproduced after switching from placebo to inclisiran. Mean LDL-C change at Day 720 was −33.7% overall. PCSK9 suppression remained stable (−71.6% overall), demonstrating durable target engagement over 2 years. Improvements in ApoB, non-HDL-C, total cholesterol and, in sensitivity analyses, Lp(a), were consistent with LDL-C findings. Modest increases in HDL-C and ApoA1 were again observed, with no effect on triglycerides or VLDL-C.

Exploratory efficacy endpoints
LDL-C reductions were consistent across genetic subgroups, including LDLR-null and LDLR-defective participants. At Day 720, 64.7% of participants achieved the recommended LDL-C target of <130 mg/dL.

Efficacy in subpopulations
Treatment effects on the primary and key secondary efficacy endpoints were generally consistent across predefined subgroups (age, sex, race, ethnicity, BMI, region, baseline statin use, LDL-C and PCSK9 levels). Placebo-adjusted LDL-C reductions at Day 330 were clinically relevant across all analysed subgroups, with greater variability observed in the placebo group due to small sample sizes. More variability was noted for Lp(a) than for other lipid parameters.

<u>HoFH (ORION-13)</u>
A total of 13 participants were randomised, 9 in the inclisiran group and 4 in the placebo group. All 13 randomised participants (100%) completed Study Part 1 and entered and completed Study Part 2. No participants discontinued study treatment during Study Part 1 or Study Part 2.
The enrolled ORION-13 study population is representative of an adolescent HoFH patient population in need of additional LDL-C lowering despite being on optimal SoC treatment. Participants were enrolled from 8 countries across Europe, USA, Canada, Asia, and the Middle East.

Primary efficacy endpoint
Inclisiran was effective in lowering LDL-C in adolescents with HoFH. The mean percent change in LDL-C from baseline to Day 330 was –21.6% in the inclisiran group and +11.7% in the placebo group, with a mean between-group difference (95% CI) of –33.25% (−59.17, −7.34). While formal hypothesis testing was not planned, the 95% CI indicates nominal statistical significance. A supplementary analysis excluding participants (n=1) on LDL-apheresis yielded consistent results.
While of variable magnitude, all participants in the inclisiran group showed a reduction in LDL-C, with the highest change being −39.7%. Responses in the placebo group were less consistent; one participant showed a large increase in LDL-C (+54.9%), while another participant showed a decrease (−15.4%).
6/9 (66.7%) participants in the inclisiran group achieved a >15% reduction in LDL-C, an improvement that is considered clinically relevant with a PCSK9-directed therapy in HoFH.

Key secondary endpoints
Secondary endpoints were consistent with the primary endpoint. Inclisiran reduced LDL-C versus placebo (time-adjusted mean difference: −34.0%) and resulted in clinically relevant reductions in ApoB, non-HDL-C, total cholesterol, and PCSK9. VLDL-C also decreased, whereas no relevant effect was observed for Lp(a); effects on triglycerides, HDL-C, and ApoA1 were small and variable.

LDL-C reductions were maintained through Day 720, with 10/13 participants (76.9%) showing decreased LDL-C and 7/13 (53.8%) achieving a >15% reduction. Reductions in ApoB, non-HDL-C, total cholesterol and PCSK9 were consistent with LDL-C findings. Sustained PCSK9 suppression was observed throughout the study.

Exploratory efficacy endpoints
Individual LDL-C response: At Day 330, >15% LDL-C reduction was achieved in 6/9 (66.7%) inclisiran-treated participants versus 1/4 (25.0%) placebo-treated participants; ≥20% and ≥30% reductions were observed in 55.6% and 33.3% of inclisiran-treated participants, respectively. At Day 720, >15%, ≥20% and ≥30% LDL-C reductions were achieved in 53.8%, 46.2% and 30.8% of participants, respectively.

Response by genotype: LDL-C reductions were generally consistent across genotype groups, with similar effects observed in LDLR defective/defective and LDLR null/defective participants.

Long-term data
In ORION-16, the data in adolescent participants with HeFH treated with inclisiran for up to 2 years showed sustained, persistent, and robust PCSK9 and LDL-C reductions, in line with the approved inclisiran label in adults, with no signs of attenuation over time.

In the inclisiran group in Study Part 1 and the placebo-inclisiran group in Study Part 2, reductions in LDL-C were observed following the first dose of inclisiran, with some further decrease seen after the second dose, which was then sustained over the remaining 1-year treatment period. In the inclisiran-inclisiran group, mean reductions in LDL-C achieved during Study Part 1 were sustained over Study Part 2, demonstrating durable efficacy over the 2-year treatment period.

In ORION-13, the data in adolescent participants with HoFH treated with inclisiran for up to 2 years showed sustained, persistent, and robust PCSK9 reductions in all participants across all study visits, with no signs of attenuation over time. In addition, sustained and persistent robust LDL-C reductions were observed in a clinically meaningful proportion of adolescents with HoFH.

The higher variability of the LDL-C response seen between visits in some participants in Study Part 2, despite consistent lowering of PCSK9, points to confounding factors, in particular irregular adherence to background lipid-lowering treatment, rather than attenuation of efficacy. Adherence to statins/lipid-lowering medications is known to be a particular challenge and may have been exacerbated in the open-label Study Part 2 when all participants were aware of their treatment with inclisiran.

4.4 Safety

The safety assessment of inclisiran in adolescents with heterozygous familial hypercholesterolaemia (HeFH) and homozygous familial hypercholesterolaemia (HoFH) is primarily based on the pivotal Phase III studies ORION-16 and ORION-13, respectively, supported by data from the ongoing extension study VICTORION-PEDS-OLE and the adult HoFH study ORION-5.

Overall, inclisiran was safe and well tolerated in adolescents, with a safety profile consistent with that previously established in adults. The most common treatment-related adverse events were mild and transient injection site reactions, representing a known adverse drug reaction of inclisiran. Rates of serious adverse events were low, comparable to placebo, and none were considered treatment-related. No deaths occurred in the paediatric studies.

No new safety signals were identified. There was no evidence of clinically relevant risks related to hepatic or renal function, musculoskeletal events, glycaemic control/diabetes, hypersensitivity, or cardiac, neurological, or psychiatric disorders. Furthermore, no adverse effects on growth, pubertal development, or hormonal maturation were observed during up to two years of treatment.

Supportive data from ORION-5 and VICTORION-PEDS-OLE were consistent with the established safety profile of inclisiran and did not reveal any new or emerging safety concerns during longer-term exposure.

In conclusion, inclisiran 300 mg administered subcutaneously on Day 1, Day 90, and every 6 months thereafter demonstrated a favourable safety profile in adolescents with HeFH and HoFH, supporting a positive benefit-risk balance in this population.

4.5 Final clinical benefit risk assessment

This benefit-risk assessment describes the benefit-risk balance of inclisiran in paediatric patients aged 12 to <18 years with HeFH or HoFH.

Medical and regulatory context

Familial hypercholesterolaemia (FH) is a genetic disorder that causes lifelong, markedly elevated LDL-C levels. If untreated, FH leads to premature cardiovascular disease. There are two clinical manifestations, HeFH and the more severe HoFH. The disease prevalence for HeFH is currently estimated to affect about 1 in every 250-300 people, whereas HoFH affects only about 1 in every 250,000-360,000 people.
Despite the availability of various lipid-lowering therapies (such as statins, ezetimibe, PCSK9 inhibitors, and ANGPTL3 inhibitors for HoFH – with evinacumab and lomitapide not even approved in Switzerland), many patients, including adolescents, fail to meet recommended LDL-C targets. Children and adolescents face specific challenges with medication adherence. Effective, early, and less burdensome LDL-lowering treatments are therefore particularly important for this patient population.
Overall, there is an unmet medical need for new treatment options for adolescents with HeFH or HoFH who are at high or very high risk of future cardiovascular events, respectively, and who require early and intensive management of hypercholesterolaemia. Effective treatments that reduce LDL-C and do not require frequent self-administration might be especially beneficial for adolescent patients.

Efficacy and respective uncertainties

Clinical pharmacology

The plasma pharmacokinetics of inclisiran and the pharmacodynamic effects on plasma PCSK9 and LDL-C had been characterised in healthy subjects and in the initially intended patient populations. In the studies on adolescents presented with this application, sparse PK sampling was conducted at pre-dose (prior to injection), 4 hours and 24 hours after the first dose of inclisiran on Day 1. Inclisiran concentrations at these timepoints were compared to those measured in adults at the same timepoints to assess any differences. Additionally, due to sparse PK sampling in ORION-16 and ORION-13, a population PK model was established using data from both adults and adolescents to estimate individual PK parameters for adolescents.

Key benefits in HeFH

The LS mean percent reduction in LDL-C from baseline to Day 330 with inclisiran was -28.5% (95% CI -35.8, -21.3) vs. placebo ($p<0.0001$) and -27.1% versus baseline. Reductions in LDL-C were observed by the first assessment following inclisiran initiation, with some further decrease seen after the second inclisiran dose, which was then sustained over the remaining treatment period. By the end of the study (Day 720), the mean (±SD) reduction in LDL-C from baseline was -33.7 ±24.0% (-32.3 ±24.8% in the inclisiran-inclisiran group and -36.4 ±22.3% in the placebo-inclisiran group). Additionally, a significant number of participants treated with inclisiran (64.7% at Day 720) achieved the recommended LDL-C target for adolescents/children. Clinically meaningful reductions in LDL-C were observed in participants treated with inclisiran, irrespective of their genetic variant group. The LDL-C-lowering effect of inclisiran was accompanied by relevant improvements in other lipids, including ApoB, non-HDL-C and total cholesterol. Consistent efficacy was seen across subgroups.

The efficacy of inclisiran is complemented by the benefit of infrequent dosing, i.e. twice a year after the initial two doses. This is particularly important for younger patients as it reduces the burden of frequent treatments. In addition to the convenient dosing scheme, inclisiran is administered by a healthcare professional (HCP). These features are particularly beneficial for adolescent patients, given the known challenges with adherence to pharmacological treatments in this age group.

Key benefits in HoFH
The primary objective of ORION-13 was to evaluate the effect of inclisiran compared to placebo on reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HoFH and elevated LDL-C. Due to the small sample size, which was based on feasibility given that HoFH is a very rare condition, the study did not include formal hypothesis testing.
Inclisiran sodium 300 mg given on Day 1, Day 90 and every 6 months thereafter was effective in lowering LDL-C in adolescents (12 to <18 years) with HoFH, including robust and sustained reductions in a clinically meaningful proportion of participants.
The mean percent reduction in LDL-C with inclisiran from baseline to Day 330 was -33.3% (95% CI -59.2, -7.3) vs. placebo and -21.6% versus baseline. While formal hypothesis testing was not planned, the 95% CI indicates nominal statistical significance. In addition, a significant number of inclisiran-treated participants achieved a >15% reduction in LDL-C.
Clinically meaningful reductions in LDL-C were observed in inclisiran-treated participants across the included genetic variant groups. Additionally, the LDL-C-lowering effect with inclisiran was accompanied by improvements in other lipids, including ApoB, non-HDL-C, and total cholesterol.
The efficacy of inclisiran is complemented by the benefit of infrequent dosing, i.e. twice a year after the initial two doses, which is especially important in younger patients by reducing the burden of frequent treatments.

Safety and respective uncertainties

Key risks in HeFH
The safety of inclisiran in adults is well characterised and has been established in a large Phase III development programme. Inclisiran was shown to be safe and well tolerated in adolescent patients with HeFH. The safety data of inclisiran in adolescents were consistent with the benign safety profile of inclisiran previously established in adult patients, including the ORION-9 study in adults with HeFH (N=482), with no new safety signals observed, including during longer-term exposure over 2 years.
No clinically relevant differences compared to placebo were seen, except for a higher incidence of injection site reactions, which is an identified adverse drug reaction (ADR) of inclisiran. All reported injection site reactions were mild, not serious and did not lead to study drug discontinuation, and all events were transient and resolved without sequelae.
No safety concerns related to hepatic or renal dysfunction, musculoskeletal events, diabetes/glycaemic control, hypersensitivity, or cardiac, neurological and psychiatric events were observed. No adverse effects regarding growth, pubertal development or hormonal status were seen with inclisiran treatment during the 2-year study period.
The longer-term safety of inclisiran in adolescents is further evaluated in an ongoing, open-label extension study, VICTORION-PEDS-OLE, with consistent safety data and no new safety signals observed at the current data cut-off.

Key risks in HoFH
In the ORION-13 study, inclisiran was shown to be safe and well tolerated in adolescent patients with HoFH. The safety data of inclisiran in adolescents were consistent with the benign safety profile of inclisiran previously established in adult patients.
No clinically relevant differences compared to placebo were seen, except for a higher incidence of injection site reactions, which is an identified ADR of inclisiran. All reported injection site reactions were mild, not serious and did not lead to study drug discontinuation, and all events were transient and resolved without sequelae.

No safety concerns related to hepatic or renal dysfunction, musculoskeletal events, diabetes/glycaemic control, hypersensitivity, or cardiac, neurological and psychiatric events were observed. No adverse effects regarding growth, pubertal development or hormonal status were seen with inclisiran treatment during the 2-year study period.
Given the small size of the ORION-13 study, which is in line with the very rare prevalence of HoFH, the safety data in adolescents with HoFH have to be seen in the context of the favourable safety data of the parallel study in adolescents with HeFH (ORION-16) as well as the already well established safety profile of inclisiran in adults. Specifically, the safety data generated from the adult study in HoFH (ORION-5) were consistent with the other Phase III studies and the overall safety profile of inclisiran in adults, with no new safety signals identified. The safety data were also consistent between the studies in adults (ORION-5) and adolescents (ORION-13) with HoFH.

Benefit-risk balance
For the treatment of paediatric patients aged 12 to less than 18 years with heterozygous familial hypercholesterolaemia or homozygous familial hypercholesterolaemia and existing atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents, the overall benefit-risk ratio of treatment with inclisiran 284 mg as a single subcutaneous injection at the start of treatment, after three months, and then every six months is **positive** based on the efficacy results and the currently available benign safety profile, if an additional reduction of LDL-C is required. Further research is needed to address the long-term safety of inclisiran in adolescents. This will be addressed in an ongoing open-label extension study (VICTORION-PEDS-OLE).

In study ORION-13, a reduction in LDL-C and other lipid parameters was observed in patients with HoFH treated with inclisiran compared to placebo. However, formal hypothesis testing was not planned in study ORION-13. Nevertheless, the 95% confidence interval indicates nominal statistical significance. The ORION-13 sample size was small due to the very rare prevalence of HoFH. While the small sample size prevented formal hypothesis testing, it permitted reliable evaluation of the difference in efficacy between groups in the primary endpoint (percent change in LDL-C at day 330), with corresponding 95% CIs. The entire 95% CI was below zero. The efficacy of inclisiran in adolescents with HoFH is supported by a favourable safety profile. The totality of the data supports the efficacy and safety of inclisiran in adolescents with HoFH (aged 12–17) as an important treatment option for this severe and difficult-to-treat condition.

Due to the lack of post-marketing experience to date in paediatric patients aged 12 and older, the PSUR requirement is being imposed again (initial PSUR obligation ended September 8th, 2025).

5 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

6 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Leqvio was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

LEQVIO

Composition

Active substances

Inclisiran (as inclisiran sodium)

Excipients

Water for injections, sodium hydroxide (for pH adjustment), 85% phosphoric acid (for pH adjustment).

Pharmaceutical form and quantity of active substance per unit

Solution for injection in pre-filled syringe (injection).
The solution is clear, colourless to pale yellow and essentially free of particulates.
Each ml contains inclisiran sodium, equivalent to 189 mg inclisiran.
Each pre-filled syringe contains 1.5 ml of solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium).

Indications/Potential uses

Hypercholesterolaemia and mixed dyslipidaemia

Leqvio is indicated in adults with hypercholesterolaemia [including heterozygous familial hypercholesterolaemia] or mixed dyslipidaemia as an adjunct to diet, and in paediatric patients 12 years of age and older with heterozygous familial hypercholesterolaemia (HeFH):

- In combination with a maximally tolerated statin dose with or without other lipid-lowering therapies in patients requiring an additional reduction in low-density lipoprotein cholesterol (LDL-C), or
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom statins are contraindicated.

Homozygous familial hypercholesterolaemia:

Leqvio is indicated as adjunct therapy to other LDL-C-lowering therapies for the treatment of paediatric patients between 12 and no more than 18 years old with homozygous familial hypercholesterolemia (HoFH).

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

Dosage/Administration

Usual dosage

Hypercholesterolaemia and mixed dyslipidaemia

The recommended dose of Leqvio for adults and paediatric patients aged 12 years and older is 284 mg as a single subcutaneous injection at the start of treatment, at 3 months and then every 6 months.

Missed treatments

If a planned treatment is missed by less than 3 months, Leqvio should be administered and the treatment regimen should resume according to the patient's original schedule.
If a planned treatment is missed by more than 3 months, a new treatment schedule should be started. Leqvio should be administered initially, again at 3 months and then every 6 months.

Treatment transition from monoclonal antibody PCSK9 inhibitors

Leqvio can be administered immediately after the last treatment with a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering, it is recommended that Leqvio is administered within 2 weeks after the last treatment with a monoclonal antibody PCSK9 inhibitor.

Special dosage instructions

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. No data are available in patients with severe hepatic impairment (see "Pharmacokinetics"). Leqvio treatment is therefore not recommended in patients with severe hepatic impairment (Child-Pugh class C).

Patients with renal impairment

No dose adjustment is necessary in patients with mild, moderate or severe renal impairment or in patients with end-stage renal disease (see "Pharmacokinetics"). There is only limited experience with Leqvio in patients with severe renal impairment. Leqvio should be used with caution in these patients.

Elderly patients

No dose adjustment is required in elderly patients (>65 years).

Children

The safety and efficacy of Leqvio in children under 12 years have not been studied. No data are available.
Method of administration
Subcutaneous use.

Leqvio is intended for subcutaneous injection into the abdomen; alternative injection sites are the upper arm or thigh. The medicinal product should not be injected into areas of active skin disease or injury such as sunburns, skin rashes, inflammation or skin infections.
Each 284 mg dose is administered using a single pre-filled syringe. Each pre-filled syringe is for single use only.
Leqvio is intended for administration by a healthcare professional.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Renal impairment

The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. As inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after Leqvio dosing.

Hepatic impairment

Patients with severe hepatic impairment (Child-Pugh class C) have not been studied (see “Pharmacokinetics”).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially “sodium-free”.

Interactions

Inclisiran is not a substrate for common drug transporters and, although *in vitro* studies were not conducted, it is not intended to be used as a substrate for cytochrome P450. Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes (including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5) or common drug transporters (including OAT1, OAT3, OCT1, OCT2, OCT3, OATP1B1, OATP1B3 or P-gp). Therefore, Leqvio is not expected to cause clinically significant interactions with other medicinal products.
Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

Pregnancy/Breast-feeding

Pregnancy

There is no or only limited experience with the use of inclisiran in pregnant women. Animal studies showed no evidence of direct or indirect reproductive toxicity (see “Preclinical data”). Leqvio should not be used during pregnancy unless the woman’s clinical condition necessitates treatment with inclisiran.

Breast-feeding

It is not known whether inclisiran is excreted into human milk. Available pharmacodynamic/toxicological data from animal studies showed that inclisiran passes into milk (see “Preclinical data”). A risk to neonates/breast-fed infants cannot be ruled out.
Therefore, a decision must be made whether to stop breast-feeding or stop/interrupt Leqvio therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of inclisiran on human fertility. Animal studies did not show any effects on fertility at exposures much higher than that sustained by patients who participated in clinical studies (see “Preclinical data”).

Effects on ability to drive and use machines

Leqvio has either no influence or only a negligible one on the ability to drive and use machines.

Adverse effects

Summary of the safety profile

Primary hyperlipidemia - Adults
According to safety data from the 3 phase III placebo-controlled pivotal studies, treatment-emergent adverse events (TEAEs) occurred at a similar incidence in patients in the inclisiran group and placebo group. The majority of TEAEs were mild and unrelated to inclisiran or placebo. The only adverse effects associated with inclisiran in the pivotal studies were adverse events at the injection site (8.2%).

Adverse effects associated with inclisiran are derived from relevant reports from three pivotal studies that included 3,655 patients with atherosclerotic cardiovascular disease (ASCVD), comparable risks (ASCVD risk equivalents) or familial hypercholesterolaemia who were treated with statins at the maximally tolerated dose and inclisiran or placebo, including 1,833 patients who received inclisiran and 1,822 patients who received placebo for up to 18 months (mean inclisiran treatment duration of 526 days) and are listed in the table below.

Adverse effects are listed according to system organ class. The frequency categories are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and unknown (frequency cannot be estimated from the available data).

General disorders and administration site conditions
Common: Adverse events at the injection site[1]

[1] See “Description of selected adverse effects”.

Description of selected adverse effects

Adverse events at the injection site

Adverse events at the injection site occurred in 8.2% and 1.8% of inclisiran-treated and placebo-treated patients, respectively, in the pivotal studies. The proportion of patients who discontinued treatment due to adverse events at the injection site in inclisiran-treated and placebo-treated patients was 0.2% and 0.0%, respectively. All of these adverse events were mild to moderate in severity, transient and resolved fully without sequelae. The most frequently occurring adverse events at the injection site in inclisiran-treated patients were injection site reactions (3.1%), injection site pain (2.2%), injection site erythema (1.6%) and injection site rash (0.7%).

Special populations

Elderly patients

Of the 1,833 patients treated with Leqvio in the pivotal studies, 981 (54%) were 65 years of age or older and 239 (13%) 75 years of age or older. No fundamental differences in safety or efficacy were observed between elderly and younger patients.

Pediatric patients (below 18 years of age)

The safety of Leqvio was assessed in two phase III studies for paediatric patients. The first study was a 24-month, two-part study of 141 patients aged between 12 and no more than 18 years of age with HeFH. It consisted of a 12-month double-blind, placebo-controlled stage followed by a 12-month open-label phase. The second study was a 24-month, two-part study involving 13 patients aged between 12 and 18 years of age with HoFH, consisting of a 12-month double-blind, placebo-controlled stage followed by a 12-month open-label one. The safety profile of Leqvio reported in these studies was consistent with the safety profile reported in adult patients and no new safety findings were observed during said studies.

Immunogenicity

During the pivotal studies, 1,830 patients were tested for anti-inclisiran antibodies. A positive test result was confirmed for 1.8% (33/1,830) of patients prior to treatment initiation and for 4.9% (90/1,830) of patients during the 18 months of treatment with inclisiran. No clinically significant differences in the clinical efficacy, safety or pharmacodynamic profile of Leqvio were observed in the patients who tested positive for anti-inclisiran antibodies.

Laboratory findings

In the phase III clinical studies there were more frequent elevations of serum hepatic transaminases between >1x the upper limit of normal (ULN) and ≤3x ULN in patients receiving inclisiran (ALT: 19.7% and AST: 17.2%) than in patients receiving placebo (ALT: 13.6% and AST: 11.1%). These elevations did not exceed the clinically relevant threshold of 3x ULN, were asymptomatic and were not associated with adverse effects or other evidence of liver dysfunction.

Reporting of suspected adverse effects

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal ElViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

No clinically relevant adverse effects were observed in healthy volunteers who received inclisiran at dosage strengths up to three times the therapeutic dose.

Treatment

There is no specific treatment for overdose with Leqvio. In the event of an overdose, the patient should be treated symptomatically and relevant supportive measures should be put in place.

Properties/Actions

ATC code

C10AX16.

Mechanism of action

Inclisiran is a cholesterol-lowering, double-stranded, small interfering ribonucleic acid (siRNA) conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by liver cells (hepatocytes). In hepatocytes inclisiran utilises the RNA interference mechanism and directs the catalytic breakdown of messenger RNA (mRNA) for proprotein convertase subtilisin/kexin type 9 (PCSK9). This increases LDL-C receptor recycling and expression on the hepatocyte surface, which increases LDL-C uptake and lowers blood LDL-C levels.

Pharmacodynamics

Following a single subcutaneous administration of 284 mg Leqvio LDL-C reduction was apparent within 14 days post dose. A mean LDL-C reduction of 49-51% was observed 30 to 60 days post dose. At day 180 LDL-C levels were reduced even more, by approximately 53%.

In the phase III studies, following four doses of Leqvio at day 1, 90, 270 and 450, LDL-C, total cholesterol, apo B, non-HDL-C and Lp(a) were reduced in patients with hypercholesterolaemia and mixed dyslipidaemia.

Cardiac electrophysiology

In a randomised, double-blind, placebo-controlled, active-comparator (moxifloxacin), 3-way crossover trial 48 healthy participants received an 852 mg subcutaneous dose of inclisiran (3 times the maximum recommended dose), moxifloxacin and placebo. No QTc prolongation or increase in any other ECG parameter was observed with the supratherapeutic dose of inclisiran.

Clinical efficacy

Clinical efficacy in hypercholesterolaemia and mixed dyslipidaemia

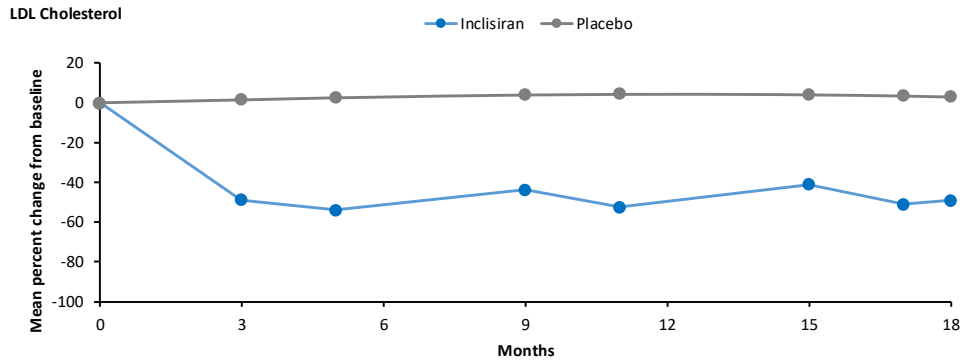
In clinical studies as well as in a number of publications, the 284 mg dose of inclisiran is equated to 300 mg inclisiran sodium salt—or is mentioned in that way.
The efficacy of inclisiran was evaluated in three phase III studies in adult patients with atherosclerotic cardiovascular disease (ASCVD) (coronary heart disease, cerebrovascular disease or peripheral arterial occlusive disease), ASCVD risk equivalents (type 2 diabetes mellitus, familial hypercholesterolaemia or 10-year risk of at least 20% of a cardiovascular event assessed by Framingham Risk Score or equivalent) and/or familial hypercholesterolaemia (FH).
Patients were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy and required additional LDL-C reduction. Approximately 17% of patients were statin-intolerant.
Patients received subcutaneous injections of 284 mg Leqvio or placebo on day 1, 90, 270 and 450.
Patients were monitored until day 540.

In the phase III pooled analysis subcutaneously administered Leqvio lowered LDL-C between 50% and 55% (Figure 1) as early as day 90, which was maintained during long-term therapy. Maximal LDL-C reduction was achieved at day 150, following a second administration. Small but statistically significant increased LDL-C reductions of up to 65% were associated with lower baseline LDL-C levels (approximately <2 mmol/l [77 mg/dl]), higher baseline PCSK9 levels and higher statin doses and statin intensity.

Reduction in LDL-C was observed across all subgroups, including age, skin colour, gender, region, body mass index, US National Cholesterol Education Program (NCEP) risk, current smoking status, baseline coronary heart disease (CHD) risk factors, family history of premature CHD, glucose tolerance status (i.e. type 2 diabetes mellitus, metabolic syndrome or neither), hypertension and baseline triglycerides.

Inclisiran also reduced non-HDL-C, apo B, total cholesterol and Lp(a) in patients with hypercholesterolaemia and mixed dyslipidaemia. There were no clinically significant changes in HDL-C and triglycerides.

Figure 1: Mean percentage change from baseline LDL-C in patients with hypercholesterolaemia or mixed dyslipidaemia treated with Leqvio compared to placebo (pooled analysis)



No. of Patients								
Placebo	1827	1796	1768	1733	1721	1695	1634	1651
Inclisiran	1833	1788	1792	1755	1741	1726	1646	1679

ASCVD and ASCVD risk equivalents

Two studies were conducted in patients with ASCVD and ASCVD risk equivalents (ORION-10 and ORION-11). Patients received a maximally tolerated dose of statin with or without other lipid-modifying therapy such as ezetimibe and required additional LDL-C reduction. Patients received subcutaneous injections of 284 mg Leqvio or placebo on day 1, 90, 270 and 450. The co-primary endpoints in each study were the percentage change in LDL-C from baseline to day 510 relative to placebo and the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 to estimate the integrated effect on LDL-C over time. Key secondary endpoints were the absolute change in LDL-C from baseline to day 510, the time-adjusted absolute change in LDL-C from baseline after day 90 and up to day 540 and the percentage change from baseline to day 510 in PCSK9, total cholesterol, apo B and non-HDL-C. Additional secondary endpoints were the individual response to Leqvio and the proportion of patients attaining global lipid targets for their ASCVD risk.

ORION-10 was a multicentre, double-blind, randomised, placebo-controlled 18-month study conducted in 1,561 patients with ASCVD.

The mean age at baseline was 66 years (age range: 35 to 90 years); 60% were ≥65 years old, 31% were women, 86% were Caucasian, 13% were Afro-American, 1% were Asian and 14% were of Spanish or Latin American origin. The mean baseline LDL-C was 2.7 mmol/l (105 mg/dl). 69% of study participants were taking high-intensity statins, 19% were taking medium-intensity statins, 1% were taking low-intensity statins and 11% were not on a statin. The most commonly administered

statins were atorvastatin and rosuvastatin. Leqvio was safe and well tolerated in the study, with adverse events leading to discontinuation of treatment in only 2.4% of Leqvio-treated patients versus 2.2% of placebo-treated patients.

Leqvio significantly reduced the mean percentage change in LDL-C from baseline to day 510 by 52% compared to placebo (95% CI: -56%, -49%; p<0.0001) (Table 1 and Figure 2).

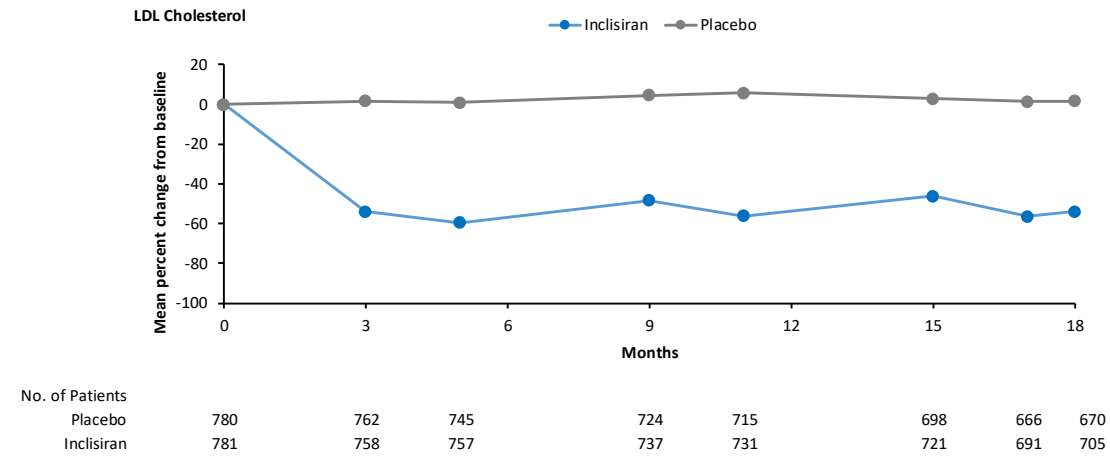
Leqvio also significantly reduced the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 by 54% compared to the placebo (95% CI: -56%, -51%; p<0.0001). For additional results see Table 1.

Table 1: Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in the ORION-10 study

Treatment group	LDL-C	Total cholesterol	Non-HDL-C	Apo B	Lp(a)*
Mean baseline value in mg/dl**	105	181	134	94	122
Day 510 (mean percentage change from baseline)					
Placebo (n=780)	1	0	0	-2	4
Leqvio (n=781)	-51	-34	-47	-45	-22
Difference from placebo (least square mean) (95% CI)	-52 (-56, -49)	-33 (-35, -31)	-47 (-50, -44)	-43 (-46, -41)	-26 (-29, -22)

* At day 540; median percentage change in Lp(a) values
** Mean baseline value in nmol/l for Lp(a)

Figure 2: Mean percentage change from baseline LDL-C in patients with hypercholesterolaemia, mixed dyslipidaemia and ASCVD treated with Leqvio compared to placebo in the ORION-10 study



At day 510 the LDL-C target of <1.8 mmol/l (70 mg/dl) was achieved by 84% of Leqvio-treated patients with ASCVD compared to 18% of placebo-treated patients.

Consistent and statistically significant (p<0.0001) reductions in percentage change in LDL-C from baseline to day 510 and time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 were observed across all subgroups, irrespective of baseline demographics, baseline disease characteristics (including gender, age, body mass index, skin colour and baseline statin use), comorbidities and geographic regions.

ORION-11 was an international, multicentre, double-blind, randomised, placebo-controlled 18-month long study involving 1,617 patients with ASCVD or ASCVD risk equivalents (ASCVD risk equivalent was defined as patients with type 2 diabetes mellitus, familial hypercholesterolaemia or a 10-year risk of 20% or greater of a cardiovascular event assessed by Framingham Risk Score or equivalent). More than 75% of patients were receiving a high-intensity statin background treatment, 87% of patients had ASCVD and 13% had a comparable risk (ASCVD risk equivalent).

The mean age at baseline was 65 years (age range: 20 to 88 years of age); 55% were ≥65 years old, 28% were women, 98% were Caucasian, 1% were Afro-American, 1% were Asian and 1% were of Spanish or Latin American origin. The mean baseline LDL-C was 2.7 mmol/l (105 mg/dl). 78% of study participants were taking high-intensity statins, 16% were taking medium-intensity statins, 0.4% were taking low-intensity statins and 5% were not on a statin. The most commonly administered statins were atorvastatin and rosuvastatin. Adverse events led to discontinuation of treatment in 2.8% of Leqvio-treated patients versus 2.2% of placebo-treated patients.

Leqvio significantly reduced the mean percentage change in LDL-C from baseline to day 510 by 50% compared to placebo (95% CI: -53%, -47%; p<0.0001) (Table 2 and Figure 3).

Leqvio also significantly reduced the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 by 49% compared to placebo (95% CI: -52%, -47%; p<0.0001). For additional results see Table 2.

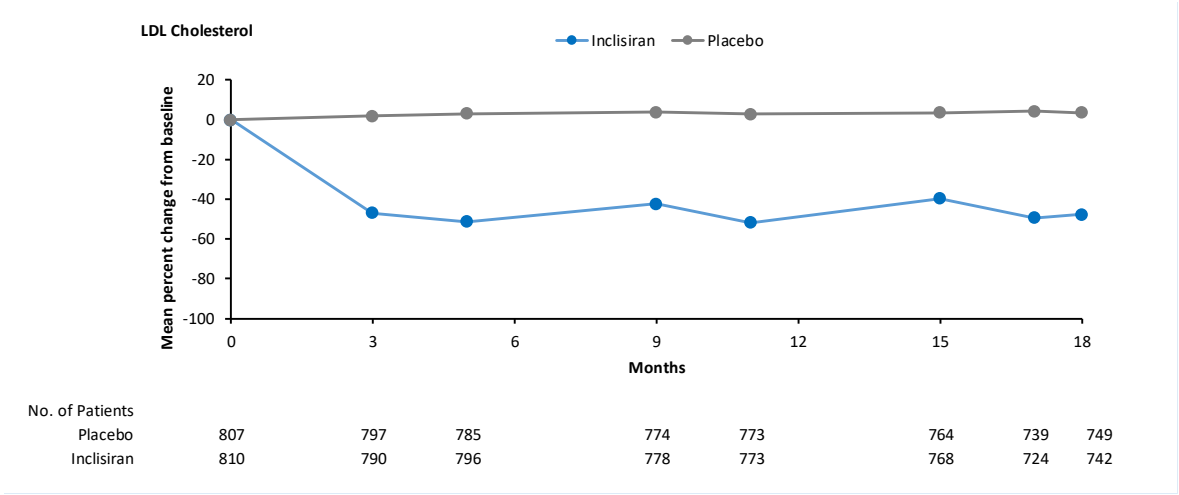
Table 2: Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in the ORION-11 study

Treatment group	LDL-C	Total cholesterol	Non-HDL-C	Apo B	Lp(a)*
Mean baseline value in mg/dl**	105	185	136	96	107
Day 510 (mean percentage change from baseline)					
Placebo (n=807)	4	2	2	1	0

Treatment group	LDL-C	Total cholesterol	Non-HDL-C	Apo B	Lp(a)*
Leqvio (n=810)	-46	-28	-41	-38	-19
Difference from placebo (least square mean) (95% CI)	-50 (-53, -47)	-30 (-32, -28)	-43 (-46, -41)	-39 (-41, -37)	-19 (-21, -16)

* At day 540; median percentage change in Lp(a) values
** Mean baseline value in nmol/l for Lp(a)

Figure 3: Mean percentage change from baseline LDL-C in patients with hypercholesterolaemia, mixed dyslipidaemia and ASCVD/ASCVD risk equivalents treated with Leqvio compared to placebo in the ORION-11 study



At day 510 the LDL-C target of <1.8 mmol/l (70 mg/dl) was achieved by 82% of Leqvio-treated patients with ASCVD compared to 16% of placebo-treated patients. In patients with an ASCVD risk equivalent, the LDL-C target of <2.6 mmol/l (100 mg/dl) was achieved by 78% of Leqvio-treated patients compared to 31% of placebo-treated patients.

Consistent and statistically significant ($p<0.05$) reductions in percentage change in LDL-C from baseline to day 510 and time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 were observed across all subgroups irrespective of baseline demographics, baseline disease characteristics (including gender, age, body mass index, skin colour and baseline statin use), comorbidities and geographic regions.

Heterozygous familial hypercholesterolaemia

ORION-9 was an international, multicentre, double-blind, randomised, placebo-controlled 18-month long study conducted in 482 patients with heterozygous familial hypercholesterolaemia (HeFH). All patients were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy such as ezetimibe and required additional LDL-C reduction. The diagnosis of HeFH was made either

by genotyping or by clinical criteria (“definite FH” using either the Simon Broome or WHO/Dutch Lipid Network criteria (DLNC)).

The co-primary endpoints were the percentage change in LDL-C from baseline to day 510 relative to placebo and the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 to estimate the integrated effect on LDL-C over time. Key secondary endpoints were the absolute change in LDL-C from baseline to day 510, the time-adjusted absolute change in LDL-C from baseline after day 90 and up to day 540 and the percentage change from baseline to day 510 in PCSK9, total cholesterol, apo B and non-HDL-C. Additional secondary endpoints were the individual response to Leqvio and the proportion of patients attaining global lipid targets for their ASCVD risk.

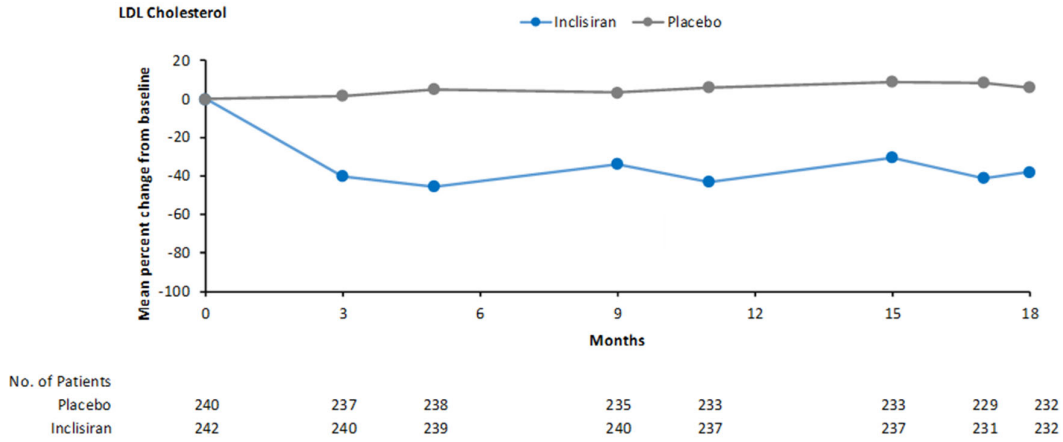
The mean age at baseline was 55 years (age range: 21 to 80 years); 22% were ≥65 years old, 53% were women, 94% were Caucasian, 3% were Afro-American, 3% were Asian and 3% were of Spanish or Latin American origin. The mean baseline LDL-C was 4.0 mmol/l (153 mg/dl). 74% of study participants were taking high-intensity statins, 15% were taking medium-intensity statins and 10% were not on a statin. 52% of patients were treated with ezetimibe. The most commonly administered statins were atorvastatin and rosuvastatin. Leqvio was safe and well tolerated in the study, with adverse events leading to discontinuation of treatment in 1% of Leqvio -treated patients versus 0% of placebo-treated patients.
Leqvio significantly reduced the mean percentage change in LDL-C from baseline to day 510 by 48% compared to placebo (95% CI: -54%, -42%; p<0.0001) (Table 3 and Figure 4).
Leqvio also significantly reduced the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 by 44% compared to placebo (95% CI: -48%, -40%; p<0.0001). For additional results see Table 3.

Table 3: Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in the ORION-9 study

Treatment group	LDL-C	Total cholesterol	Non-HDL-C	Apo B	Lp(a)*
Mean baseline value in mg/dl**	153	231	180	124	121
Day 510 (mean percentage change from baseline)					
Placebo (n=240)	8	7	7	3	4
Leqvio (n=242)	-40	-25	-35	-33	-13
Difference from placebo (least square mean) (95% CI)	-48 (-54, -42)	-32 (-36, -28)	-42 (-47, -37)	-36 (-40, -32)	-17 (-22, -12)

* At day 540; median percentage change in Lp(a) values
** Mean baseline value in nmol/l for Lp(a)

Figure 4: Mean percentage change from baseline LDL-C in patients with hypercholesterolaemia, mixed dyslipidaemia and heterozygous familial hypercholesterolaemia treated with Leqvio compared to placebo in the ORION-9 study



At day 510, 52.5% of Leqvio-treated patients with ASCVD achieved their LDL-C target of <1.8 mmol/l (70 mg/dl) compared to 1.4% of placebo-treated patients with ASCVD, while 66.9% of Leqvio-treated patients with ASCVD risk equivalents achieved their LDL-C target of <2.6 mmol/l (100 mg/dl) compared to 8.9% of placebo-treated patients with ASCVD risk equivalents.

Consistent and statistically significant ($p<0.05$) reductions in percentage change in LDL-C from baseline to day 510 and time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 were observed across all subgroups irrespective of baseline demographics, baseline disease characteristics (including gender, age, body mass index, skin colour and baseline statin use), comorbidities and geographic regions.

Paediatric clinical studies

Heterozygous Familial Hypercholesterolemia (HeFH)

ORION-16 was a 24-month, two-part study consisting of a 12-month randomised, double-blind, placebo-controlled stage (Part 1/Year 1), followed by a 12-month open-label one (Part 2/Year 2) during which all patients received inclisiran. ORION-16 enrolled 141 paediatric patients aged between 12 and <18 years with HeFH and elevated LDL-C. Most patients were taking statins with or without other LDL-C-lowering therapies.
During Year 1, patients were randomised in a 2:1 ratio and were administered subcutaneous injections of 284 mg of Leqvio (n=93) or placebo (n=48) on Day 1, Day 90 and Day 270. The primary endpoint was the percentage change in LDL-C from baseline to Day 330. The secondary endpoints included time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330, and

the percent change in LDL-C, Apo B, non-HDL-C, total cholesterol, and PCSK9 from baseline to each assessment time up to Day 720 [12].

Leqvio significantly reduced the mean percentage change in LDL-C from baseline to Day 330 by 29% compared to placebo (95% CI: -36%, -21%; p<0.0001) (Table 4) [12].

Leqvio also significantly reduced the time-adjusted mean-percentage change in LDL-C from baseline between Day 90 and Day 330 by 29% compared to placebo (95% CI: -36%, -22%; p<0.0001). The mean percentage change in PCSK9 from baseline to Day 330 was -73% in the inclisiran group and 5% in the placebo group. For additional results, see Table 4.

Table 4 Mean percentage change from baseline and difference from placebo in lipid parameters at day 330 in patients with HeFH in ORION-16

Treatment Group	LDL-C	Apo B	Non-HDL-C	Total Cholesterol
Day 330 (mean percentage change from baseline)				
Placebo (n=48)	1	4	2	0
Inclisiran (n=93)	-27	-21	-25	-19
Difference from placebo (LS Mean) (95% CI)	-29 (-36, -21)	-26 (-32, -20)	-27 (-34, -20)	-19 (-25, -14)

Apo B = Apolipoprotein B; CI = Confidence interval; LDL-C = Low-density lipoprotein cholesterol; LS = Least squares/mean; Non-HDL-C = Non-high-density lipoprotein cholesterol.

In the Year 2 open-label single-arm follow-up stage, all patients were administered subcutaneous injections of 284 mg of Leqvio. The percent change in LDL-C from baseline (randomisation in double-blind part) on Day 720 was -34% (24%) (mean, SD) and -36% (-49, -21) (median, Q1, Q3). The mean percent change in PCSK9 from baseline (randomization in double-blind part) was -72% on Day 720 [12].

Homozygous Familial Hypercholesterolemia (HoFH)

ORION-13 was a 24-month, two-part study consisting of a 12-month randomized, double-blind, placebo-controlled part (Part 1/Year 1), followed by a 12-month open-label part (Part 2/Year 2) during which all patients received inclisiran. ORION-13 enrolled 13 paediatric patients aged 12 to <18 years with HoFH and elevated LDL-C. All patients were taking statins with or without other LDL-C-lowering therapies. Patients with a null (negative) variant in both low-density lipoprotein receptor (LDLR) alleles, who were considered unlikely to benefit from a reduction in PCSK9, were excluded.

In Year 1, patients were randomised in a 2:1 ratio and were administered subcutaneous injections of 284 mg of Leqvio (n=9) or placebo (n=4) on Day 1, Day 90 and Day 270. The primary endpoint was the percentage change in LDL-C from baseline to Day 330. The secondary endpoints included time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330, and the percent change in LDL-C, Apo B, non-HDL-C, total cholesterol, and PCSK9 from baseline to each assessment time up to Day 720 [12].

Leqvio reduced the mean percentage change in LDL-C from baseline to Day 330 by 33% compared to placebo (95% CI: -59%, -7%) (Table 5).
Leqvio also reduced the time-adjusted mean-percentage change in LDL-C from baseline after Day 90 and up to Day 330 by 34% compared to placebo (95% CI: -68%, 0%). The mean percentage change in PCSK9 from baseline to Day 330 was -65% in the inclisiran group and -5% in the placebo group. For additional results, see Table 5.

Table 5 Mean percentage change from baseline and difference from placebo in lipid parameters at day 330 in patients with HoFH in ORION-13

Treatment Group	LDL-C	Apo B	Non-HDL-C	Total Cholesterol
Day 330 (mean percentage change from baseline)				
Placebo (n=4)	12	5	9	9
Inclisiran (n=9)	-22	-19	-23	-19
Difference from placebo (Mean) (95% CI)	-33 (-59, -7)	-23 (-40, -6)	-33 (-60, -6)	-28 (-52, -4)

Apo B = Apolipoprotein B; CI = Confidence interval; LDL-C = Low-density lipoprotein cholesterol; LS = Least squares-mean; Non-HDL-C = Non-high-density lipoprotein cholesterol.

In the Year 2 open-label single-arm follow-up part, all patients were administered subcutaneous injections of 284 mg of Leqvio. The percent change in LDL-C from baseline (randomisation in double-blind part) on Day 720 was -13% (28%) (mean, SD) and -19% (-35, -1) (median, Q1, Q3). The mean percent change in PCSK9 from baseline (randomisation in double-blind part) was -64% on Day 720.

Pharmacokinetics

Absorption

Following a single subcutaneous administration, systemic exposure to inclisiran increased in a linear and dose-proportional manner over a range from 24 mg to 756 mg. At the recommended dosing regimen of 284 mg, plasma concentrations reached their peak approximately 4 hours post dose with a mean C_{max} of 509 ng/ml. Concentrations fell to undetectable levels within 48 hours post dose. The mean area under the plasma concentration-time curve from dosing extrapolated to infinity ($AUC_{0\text{-}inf}$) was 7,980 ng*h/ml. Pharmacokinetic findings after multiple subcutaneous administrations of inclisiran were similar to single-dose administration.

Distribution

Based on *in vitro* investigations inclisiran is 87% bound to plasma proteins at the relevant clinical plasma concentrations. Following a single subcutaneous 284 mg dose of inclisiran in healthy adults the apparent volume of distribution is approximately 500 l. Based on non-clinical data inclisiran has

been shown to have high uptake into and selectivity for the liver, the target organ for cholesterol lowering.

Metabolism

Based on *in vitro* investigations inclisiran is primarily metabolised by nucleases to shorter, inactive nucleotides of varying length. Inclisiran is not a substrate for common drug transporters and, although *in vitro* studies were not conducted, it is not intended to be used as a substrate for cytochrome P450.

Elimination

The terminal elimination half-life of inclisiran is approximately 9 hours and no accumulation occurs with multiple dosing. 16% of an inclisiran dose of 284 mg is cleared through the kidney.

Linearity/non-linearity

After subcutaneous administration of single inclisiran doses ranging from 24 mg to 756 mg, an approximately dose-proportional increase in inclisiran exposure was observed. No accumulation and no time-dependent changes were observed after multiple subcutaneous doses of inclisiran.

Pharmacokinetic/pharmacodynamic relationships

A dissociation was observed between inclisiran pharmacokinetic parameters in the plasma and the pharmacodynamic effects on plasma levels of PCSK9 and LDL-C. The observed long duration of action on PCSK9 and LDL-C does not correlate with the plasma elimination half-life of inclisiran, which consists of 9 hours. A maximum reduction of PCSK9 and LDL-C was observed with a 284 mg dose. Higher doses did not lead to greater effects.

Pharmacokinetics in special populations

Paediatric patients (below 18 years)

The pharmacokinetics of inclisiran were evaluated in 40 paediatric patients with HeFH (ORION-16) and 9 pediatric patients with HoFH (ORION-13) aged between 12 and 18 years old. The results showed that variability in inclisiran plasma concentrations was low to moderate. Inclisiran concentrations in paediatric patients at 4 hours and 24 hours after a 284 mg single dose were similar to concentrations in adults.

Hepatic impairment

The pharmacokinetic analysis of data from a dedicated hepatic impairment study showed an increase in inclisiran C_{max} and AUC of 1.1- and 1.3-fold in patients with mild hepatic impairment (Child-Pugh A, n=10) compared to patients with normal hepatic function (n=12). Despite the higher inclisiran plasma exposures, the reduction in LDL-C was similar in patients with normal hepatic function and mild hepatic impairment.

In patients with moderate hepatic impairment (Child-Pugh B, n=6) the C_{max} and AUC of inclisiran were increased 2.1- and 2.0-fold, baseline PCSK9 levels were markedly lower and the mean percentage change in LDL-C from baseline was reduced by 40% in patients with moderate hepatic impairment compared to a 52% reduction in patients with normal hepatic function.
Leqvio has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment

The pharmacokinetic analysis of data from a dedicated renal impairment study showed an increase in inclisiran C_{max} and AUC of 2.3-, 2.0- and 3.3-fold and 1.6-, 1.8- and 2.3-fold, respectively, in patients with mild, moderate or severe renal impairment relative to patients with normal renal function. The maximum percentage changes in LDL-C from baseline were 58%, 35%, 53% and 51% in patients with normal renal function and patients with mild, moderate or severe hepatic impairment, respectively.
Despite the higher transient plasma exposures over 24 to 48 hours the reduction in LDL-C was similar across all renal function groups.
The effect of end-stage renal disease or haemodialysis on inclisiran pharmacokinetics has not been studied.

Other special populations

A population pharmacodynamic analysis was conducted on data from 4,328 patients. Age, body weight, gender, ethnicity and creatinine clearance did not significantly influence inclisiran pharmacodynamics.

Preclinical data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, chronic toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity.

Long-term toxicity (repeated-dose toxicity)

In repeated-dose toxicology studies conducted in rats and monkeys the No Observed Adverse Effect Levels (NOAELs) were determined as the highest doses administered subcutaneously and were associated with a safety margin many times higher than exposure in humans at the clinical dose.

Mutagenicity

No mutagenic or clastogenic potential of inclisiran was found in a battery of tests, including a bacterial mutagenicity assay, an *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes and an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

Inclisiran was not carcinogenic in Sprague-Dawley rats or TgRasH2 mice administered inclisiran at doses considerably higher than clinical doses.

Reproductive toxicity

Reproduction studies with rats and rabbits revealed no evidence of foetal harm due to inclisiran at the highest administered doses, leading to exposure significantly over the maximum human exposure.

Inclisiran did not impair the fertility or reproductive performance of male and female rats exposed to inclisiran before and during gestation. The doses were associated with systemic exposures many times higher than the human exposure at clinical doses.

Inclisiran has been detected in the milk of lactating rats; however, there is no evidence of systemic absorption in suckling rat neonates.

Other information

Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use after the expiry date (= EXP) printed on the container.

Special precautions for storage

Do not store above 25°C. Do not freeze.
Keep out of the reach of children.

Instructions for use and handling

Leqvio should be inspected visually prior to administration. The solution must be clear, colourless to pale yellow and essentially free of particulates. If the solution contains visible particulates, it must not be used.
Any unused medicinal product or waste material must be disposed of in accordance with national requirements.

Swissmedic number

67836 (Swissmedic)

Pack sizes

1.5 ml solution in pre-filled syringe (type I glass) with plunger stopper (bromobutyl, FluroTec-coated rubber), with needle and rigid needle cap. [B]

1.5 ml solution in pre-filled syringe (type I glass) with plunger stopper (bromobutyl, FluroTec-coated rubber), with needle and rigid needle cap, with needle guard. [B]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

Information last revised

July 2026