Summary Report of Benefit-Risk Assessment

LEQVIO SOLUTION FOR INJECTION IN PREFILLED SYRINGE 284 MG/1.5 ML
NEW DRUG APPLICATION

Active Ingredient(s)	Inclisiran
Product Registrant	Novartis
Product Registration Number	SIN16295P
Application Route	Full evaluation
Date of Approval	3 Aug 2021

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A INTRODUCTION

Leqvio is indicated for the treatment of adults with primary hypercholesterolaemia (including heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet. It may be used in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach low density lipoprotein-C (LDL-C) goals with the maximum tolerated dose of a statin. It may also be used alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The active substance, inclisiran, is a double-stranded small interfering ribonucleic acid (siRNA) conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes through binding to liver-expressed asiaglycoprotein receptors (ASGPR). In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for proprotein convertase subtilisin/kexin type 9 (PCSK9). This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.

Leqvio is available as a solution for injection in pre-filled syringe containing 284 mg of inclisiran (equivalent to 300mg of inclisiran sodium salt) in 1.5 ml solution. Other ingredients in the formulation include water for injections as the diluent, and sodium hydroxide and phosphoric acid for pH adjustment.

B ASSESSMENT OF PRODUCT QUALITY

Drug substance:

Inclisiran sodium is a synthetic, chemically modified, double-stranded siRNA. Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for Agilent Technologies Inc was adequate to support the approved storage condition and re-test period. The packaging is high density polyethylene (HDPE) bottle with a screw polypropylene (PP) lid closure. The HDPE bottle is then placed into a tri-layered foil and vacuum sealed to protect from moisture. The drug substance is approved for storage at -20°C with a re-test period of 36 months.

Drug product:

The drug product is a sterile solution in a prefilled syringe (PFS). The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at or below 25 ºC. The container closure system is a type I clear glass syringe with a staked needle and rigid needle shield, sealed with a bromobutyl plunger.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of inclisiran was based on three pivotal studies, ORION-9, ORION-10 and ORION-11. These were Phase 3, randomised, double-blind, placebo-controlled studies in which inclisiran was administered as adjunctive treatment to maximally tolerated statin therapy. ORION-9 was conducted in patients with heterozygous familial hypercholesterolaemia (HeFH), ORION-10 included patients with atherosclerotic cardiovascular disease (ASCVD), and ORION-11 included patients with ASCVD or ASCVD risk equivalents. The ASCVD risk equivalent population comprised patients with type 2 diabetes, familial hypercholesterolaemia, and/or a 10-year risk of 20% or greater of having a cardiovascular event assessed by Framingham Risk Score or equivalent.

A total of 3660 patients (482, 1561 and 1617 patients in ORION-9, 10 and 11 respectively) across the three studies were randomised in a 1:1 ratio to receive subcutaneous injections of 284mg of inclisiran or placebo on Day 1, Day 90 and Day 450, and were followed until Day 540. The co-primary endpoints were the percentage change from baseline to Day 510, and time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. The 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.

The majority of patients were White (92.3%), male (67.5%) with a median age of 66 years. Across the Phase 3 studies, 84.9% had ASCVD and 15.1% had ASCVD risk-equivalents including HeFH. 94% of all patients were on statins at study entry, with those on high-intensity statins making up 74% of the study population.

The mean baseline LDL-C for patients in studies ORION-10 and 11 was 105 mg/dL and 153 mg/dL in study ORION-9. 19.2% of patients had baseline triglyceride levels of ≥200 mg/dL, and 17.8% of patients were either partially (10.1%) or completely intolerant (7.7%) to statins. The latter group of patients was either on non-statins (e.g. ezetimibe) or not on any lipid-modifying therapy.

In ORION-9, inclisiran 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) in patients with HeFH. Inclisiran 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).

Statistically significant improvements in the co-primary endpoints were also demonstrated in patients with ASCVD or ASCVD equivalents (Studies ORION-10 and 11). The mean percentage change in LDL-C from baseline to Day 510 were -52% (95% CI: -56%, -49%; p<0.0001) and -50% compared to placebo (95% CI: -53%, -47%; p<0.0001), respectively. The reductions in time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 were -54% (95% CI: -56%, -51%; p<0.0001) and -49% (95% CI: -52%, -47%; p<0.0001), respectively.

The co-primary endpoints were supported by consistent and statistically significant results of the key secondary endpoints. Improvements in LDL-C were consistent across subgroups stratified by age, race, metabolic disease, baseline BMI and baseline LDL-C. The percentage LDL-C reduction from baseline to Day 510 vs placebo was comparable between patients with baseline triglycerides <200mg/dL (-53%) and ≥200 mg/dL (-57%). In statin-intolerant patients who were treated with inclisiran alone or in combination with other lipid-modifying therapies, the percentage LDL-C reduction was -49% compared to -55% in patients without statin-intolerance.

Summary of results of co-primary endpoints in Phase 3 studies

	ORION-9		ORION-10		ORION-11	
	Placebo (n=240)	Inclisiran (n=242)	Placebo (n=780)	Inclisiran (n=781)	Placebo (n=807)	Inclisiran (n=810)
Percentage change in LDL-C from baseline to Day 510/%	8	-40	1	-51	4	-46
LS Mean difference vs placebo (95% CI)	-	-48 (-54, -42)*	-	-52 (-56,-49)*	-	-50 (-53, -47)*
Time-adjusted percentage change in LDL-C from Day 90 up to Day 540/%	6	-38	3	-51	3	-46
LS Mean difference vs placebo (95% CI)	-	-44 (-48, -40)*	-	-54 (-56, -51)*		-49 (-52, -47)*

*p<0.0001

Summary of results of key secondary endpoints in Phase 3 studies

	ORION-9		ORION-10		ORION-11	
	Placebo (n=240)	Inclisiran (n=242)	Placebo (n=780)	Inclisiran (n=781)	Placebo (n=807)	Inclisiran (n=810)
Absolute change in LDL-C from baseline to Day 510(mg/dL)	10	-59	-2	-56	1	-51
LS Mean difference vs placebo (95% CI)	-	-69 (-77, -61)*	-	-54 (-57, -51)*	-	-52 (-55, -49)*
Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 (mg/dL)	6	-57	0	-54	0	-49

LS Mean difference vs placebo (95% CI)	-	-63 (-69, -56)*	-	-53 (-56, -51)*	-	-49 (-51, -46)*
Percentage change in PCSK9 from baseline to Day 510	18	-61	14	-70	16	-64
LS Mean difference vs placebo (95% CI)	-	-78 (-83, -73)*	-	-83 (-89, -77)*	-	-79 (-82 -77)*
Percentage change in Total cholesterol from baseline to Day 510	7	-25	0	-34	2	-28
LS Mean difference vs placebo (95% CI)	-	-32 (-36, -28)*	-	-33 (-35, -31)*	-	-30 (-32, -28)*
Percentage change in Apo-B from baseline to Day 510	3	-33	-2	-45	1	-38
LS Mean difference vs placebo (95% CI)	-	-36 (-40, -32)*	-	-43 (-46.-41)*	-	-39 (-41, -37)*
Percentage change in Non-HDL-C from baseline to Day 510	7	-35	0	-47	2	-41
LS Mean difference vs placebo (95% CI)	-	-42 (-47,-37)*	-	-47 (-50, -44)*	-	-43 (-46, -41)*

*p<0.0001

Efficacy was demonstrated for the co-primary and key secondary endpoints in the three pivotal studies. There was adequate representation of patients with elevated baseline triglycerides ≥200 mg/dL (mixed dyslipidaemia) as well as statin-intolerant patients, and the results from these subgroups demonstrated comparable efficacy to the overall population.

The indication sought in the application for primary hypercholesterolemia may include non-FH patients without ASCVD or ASCVD equivalents who were not investigated in the clinical studies. However, given the mechanism of action of inclisiran which degrades PCSK9 mRNA intracellularly in hepatocytes, the binding of inclisiran to the ASGPR and its subsequent uptake into these cells is not expected to differ from the studied populations. As a result, the extent of PCSK9 inhibition is also expected to be similar.

Hence, efficacy and safety of inclisiran could be reasonably extrapolated to this patient population and the indication of primary hypercholesterolemia (including heterozyqous familial and non-familial) or mixed dyslipidaemia in patients with or without statin intolerance is considered acceptable.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of inclisiran was based primary on safety data derived from the three Phase 3 studies (ORION-9, 10, 11), which included 3655 patients (1833 inclisiran and 1822 placebo). The mean treatment duration for patients exposed to inclisiran and placebo was 526 and 523 days respectively.

Overview of safety profile

Adverse event (AE)	Placebo (n=1822)	Inclisiran (n=1833)
At least 1 treatment-related AE (TEAE)	1409 (77.3%)	1430 (78.0%)
At least 1 treatment-related Serious AE (SAE)	429 (23.0%)	374 (20.4%)
At least 1 related SAE	5 (0.3%)	2 (0.1%)
Discontinuations due to TEAE	5 (0.3%)	12 (0.7%)
Deaths due to AE	27 (1.5%)	27 (1.5%)

A total of 77.3% placebo-treated and 78.0% inclisiran-treated patients experienced at least 1 TEAE. The most common TEAEs that occurred more frequently in the inclisiran-treated patients compared to placebo were diabetes mellitus (11.6% vs 11.4%), nasopharyngitis (7.6% vs 7.4%), arthralgia (5.0% vs 4.0%), back pain (4.5% vs 4.2%), urinary tract infection (4.4% vs 3.6%), diarrhoea (3.9% vs 3.5%), bronchitis (4.3% vs 2.7%), cough (3.3% vs 3.0%), headache (3.2% vs 3.1%), angina pectoris (3.2% vs 3.1%), dizziness (3.2% vs 3.0%), pain in extremity (3.3% vs 2.6%), dyspnoea (3.2% vs 2.6%), and injection site reaction (3.1% vs 0.1%).

The incidences of SAEs in inclisiran and placebo patients were 20.4% and 23.0% respectively. The most commonly reported SAEs were coronary artery disease (1.3% vs 1.8%), acute myocardial infarction (1.1% vs 1.7%), angina pectoris (1.1% each), angina unstable (0.9% vs 1.4%), pneumonia (1.1% vs 0.9%) and atrial fibrillation (1.1% vs 0.8%).

The incidences of AEs leading to discontinuation in inclisiran and placebo patients were 0.7% and 0.3% respectively. The most common AE leading to treatment discontinuation in the inclisiran arm was injection site reactions (0.2% vs 0.0%). The rates of deaths were 1.5% in both inclisiran and placebo arms, with cardiac disorders (0.7% vs 0.5%) reported as the most common cause of death. These were considered to be related to the underlying disease condition and not due to study treatment.

The AEs of special interest (AESI) included injection site AEs, impaired glucose control and elevation of liver transaminases. AEs at the injection site occurred in 8.2% and 1.8% of inclisiran-treated and placebo-treated patients, respectively. These include injection site reaction (3.1%), pain (2.2%), erythema (1.6%) and rash (0.7%) in the inclisiran arm. The majority of AEs were mild or moderate in severity, transient and resolved without sequalae.

An analysis of the shift in glucose control based on both fasting glucose and haemoglobin A1c (HbA1c) revealed that a greater proportion of inclisiran-treated patients vs placebo had shifts from normal to impaired (15.3% vs 13.3%) and impaired to diabetes (9.2% vs 8.0%). There were more frequent elevations of serum hepatic transaminases between >1x the upper limit of normal (ULN) and ≤3x ULN in patients on inclisiran vs placebo (alanine aminotransferase (ALT): 19.7% vs 13.6% and aspartate aminotransferase (AST): 17.2% vs 11.1%). These AESIs have been described in the proposed package insert. In addition, the applicant is

required to submit periodic benefit-risk evaluation reports to HSA as part of ongoing safety monitoring.

Overall, the safety profile of inclisiran in the treatment of primary hypercholesterolaemia or mixed dyslipidaemia was considered acceptable. Appropriate warnings and precautions in the product labelling as well as ongoing safety monitoring have been put in place to mitigate the potential long-term safety concerns.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Statins remain the standard of care for primary hypercholesterolemia. Despite significant progress over the years, there remains a need for additional therapies that reduce LDL-C in patients with an inadequate response to maximally-tolerated statins or could not tolerate statins.

Inclisiran, alone or in combination with maximally-tolerated statins, demonstrated statistically significant and sustained reductions in LDL-C from baseline across a broad population of primary hypercholesterolaemia patients including HeFH, ASCVD and ASCVD risk equivalents. The percentage reduction of LDL-C from baseline compared to placebo at Day 510 ranged from 48% to 52% in the three studies. Consistent results were demonstrated for the co-primary endpoint time-adjusted percentage change in LDL-C from Day 90 up to Day 540 (-44% to -54%), as well as for key secondary endpoints including percentage change from baseline in PCSK9 (-78% to -83%). The efficacy and safety of inclisiran in various subpopulations, including mixed dyslipidaemia, non-FH and statin-intolerant patients were consistent with the overall population.

Inclisiran was generally well-tolerated. Most AEs were mild to moderate and generally manageable. Notable safety concerns such as elevated liver enzymes, injection site reactions and impaired glucose have been adequately described in the package insert. The long-term safety of inclisiran post-approval would continue to be monitored as part of the local risk management program.

Overall, the benefits of inclisiran with respect to the clinically meaningful and statistically significant reduction in LDL-C outweighed the risks in the treatment of primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk profile of Leqvio for the treatment of primary hypercholesterolaemia (including heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, is considered favourable and approval of the product registration was granted on 3 Aug 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

NOVARTIS

1 Tradename

LEQVIO™ solution for injection in pre-filled syringe

2 Description and composition

Pharmaceutical form

Leqvio is supplied as a solution for injection. The solution is clear, colorless to pale yellow and essentially free of particulates.

Active substance

Each mL contains inclisiran sodium equivalent to 189 mg of inclisiran.

Each pre-filled syringe contains 1.5 mL of solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium).

Excipients

Water for injection

Sodium hydroxide (for pH adjustment)

Phosphoric acid (for pH adjustment)

Information might differ in some countries.

3 Indications

Treatment in adults with primary hypercholesterolaemia (including 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.

4 Dosage regimen and administration

Dosage regimen

The recommended dose of Leqvio is 284 mg administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months.

Missed dose

- If a planned dose of Leqvio is missed by less than 3 months, Leqvio should be administered and dosing maintained according to the patient's original schedule.

- If a planned dose of Leqvio is missed by more than 3 months, a new dosing schedule should be started – Leqvio should be administered initially, again at 3 months, followed by every 6 months.

Treatment Transition from PCSK9 Inhibitor Monoclonal Antibody

Leqvio can be administered immediately after the last dose of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor monoclonal antibody. To maintain LDL-C lowering, it is recommended that Leqvio is administered within 2 weeks after the last dose of a PCSK9 inhibitor monoclonal antibody.

Special populations

Renal impairment

No dose adjustment is necessary for patients with renal impairment (mild, moderate or severe) or end-stage renal disease. There is limited experience with inclisiran in patients with severe renal impairment. Inclisiran should be used with caution in these patients. If administering Leqvio to patients on hemodialysis, hemodialysis should not be performed for at least 72 hours after Leqvio dosing (see section 11 Clinical pharmacology).

Hepatic impairment

No dose adjustment is necessary for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

Pediatric patients (below 18 years)

The safety and efficacy of Leqvio in patients below 18 years of age have not been established.

Geriatric patients (65 years of age or above)

No dose adjustment is necessary in patients 65 years of age or above.

Method of administration

Leqvio is intended for administration by a healthcare professional.

Leqvio is for subcutaneous injection into the abdomen. Injections should not be given into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

Leqvio should be inspected visually for particulate matter prior to administration. If the solution contains visible particulate matter, the solution should not be used.

Each 284 mg dose is administered using a single pre-filled syringe. Each pre-filled syringe is for single use only.

5 Contraindications

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

6 Warnings and precautions

None.

7 Adverse drug reactions

Summary of the safety profile

The safety of Leqvio was evaluated in 3 Phase III placebo-controlled trials that included 3,655 patients with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalents, or familial hypercholesterolemia, treated with maximally tolerated statins and Leqvio or placebo, including 1,833 patients exposed to inclisiran for up to 18 months (mean treatment duration of 526 days).

Safety data from the 3 Phase III placebo-controlled pivotal trials showed that treatment-emergent adverse events (TEAEs) occurred at a similar incidence in the Leqvio -treated and placebo-treated patients. The majority of the TEAEs were mild and unrelated to Leqvio or placebo. The only adverse reactions associated with Leqvio in pivotal trials were adverse events at the injection site.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 7-1 Adverse drug reactions reported in patients treated with inclisiran

Adverse drug reactions	Placebo (N=1822) %	Tradename (N=1833) %	Frequency category
General disorders and administration site conditions			
Adverse events at the injection site[1]	1.8	8.2	Common

[1]Most frequently occurring adverse events are: injection site reaction, injection site pain, injection site erythema, and injection site rash.

Description of selected adverse drug reactions

Adverse events at the injection site

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

Immunogenicity

In the pivotal trials, 1,830 patients were tested for anti-drug antibodies. Confirmed positivity was detected in 1.8% (33/1830) of patients prior to dosing and in 4.9% (90/1830) of patients during the 18 months of treatment with Leqvio. No clinically significant differences in the clinical efficacy, safety or pharmacodynamic profiles of Leqvio were observed in the patients who tested positive for anti-inclisiran antibodies.

Liver enzymes

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 on inclisiran (ALT: 19.7% and AST: 17.2%) than in patients on placebo (ALT: 13.6% and AST: 11.1%). These elevations did not progress to exceed the clinically relevant threshold of 3x ULN, were asymptomatic and were not associated with adverse reactions or other evidence of liver dysfunction.

Glycemic control

There were no clinically meaningful differences between placebo-treated and inclisiran-treated subjects in shift from baseline in glucose control categories based on fasting plasma glucose and HbA1c. Shifts in glycemic control from normal to impaired and impaired to diabetes in the inclisiran arm compared to placebo arm were 15.3% vs. 13.3% and 9.2% vs. 8.0%, respectively.

8 Interactions

Leqvio is not a substrate, inhibitor or inducer of cytochrome P450 (CYP450) enzymes or common drug transporters, and therefore Leqvio is not expected to have clinically significant interactions with other medications. Drug-drug interaction assessments demonstrated a lack of clinically meaningful interactions with either atorvastatin, rosuvastatin or other statins (see section 11 Clinical pharmacology).

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

There are no available data on the use of Leqvio in pregnant women to inform a drug associated risk. Animal reproduction studies in rats and rabbits have not shown risk of increased fetal abnormalities with subcutaneous administration of inclisiran during organogenesis at doses equivalent to 16- to 39-fold the maximum recommended human dose (MRHD) based on AUC (see Animal data). As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy.

Animal data

In embryo-fetal development studies conducted in pregnant female Sprague-Dawley rats and New Zealand White rabbits, inclisiran was administered by subcutaneous injection at 50, 100 and 150 mg/kg once daily during the period of organogenesis (rats: Days 6 to 17 post coitum; rabbits: Days 7 to 19 post coitum). There was no evidence of embryo-fetal death, fetotoxicity or teratogenicity. The highest doses tested were associated with safety margins in rats and rabbits of 16.0-fold and 39.3-fold, respectively, based on AUC, compared to exposures observed at the MRHD.

In rats, inclisiran was detected in fetal plasma; the concentrations generally increased with increasing dose, but were markedly (65- to 154-fold) lower compared to maternal levels. There was no inclisiran detected in fetal livers in any dose group. In rabbits, inclisiran was below the lower limit of quantitation in fetal plasma as well as liver.

In the pre- and post-natal development study conducted in pregnant female Sprague-Dawley rats, inclisiran was administered once daily by subcutaneous injection at 50, 100 and 150 mg/kg from Day 6 post coitum to lactation Day 20. Inclisiran was well-tolerated with no evidence of maternal toxicity and no effects on maternal performance. There were no adverse effects on the offspring.

9.2 Lactation

Risk summary

It is not known if inclisiran is transferred into human milk after administration of Leqvio. There are no data on the effects of inclisiran on the breastfed child or on milk production. Inclisiran was present in rat milk following once-daily subcutaneous injection. However, there is no evidence of systemic absorption in suckling rat neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Leqvio and any potential adverse effects on the breastfed child from Leqvio.

9.3 Females and males of reproductive potential

Infertility

There are no data on the effect of Leqvio on human fertility. No effects on fertility were observed in female and male rats at doses equivalent to 20.4-fold and 44.1-fold based on AUC, compared to exposures observed at the MRHD (see section 13 Non-clinical safety data).

10 Overdosage

No clinically relevant adverse effects were observed in healthy volunteers who received inclisiran at doses up to three times the therapeutic dose. No specific treatment for Leqvio overdose is available. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Other lipid-modifying agents, ATC code: C10AX16.

Mechanism of action (MOA)

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 hepatocytes. In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.

Pharmacodynamics (PD)

Following a single subcutaneous administration of 284 mg of Leqvio, LDL-C reduction was apparent within 14 days post-dose. Mean reductions of 49%-51% for LDL-C were observed 30 to 60 days post-dose. At Day 180, LDL-C levels were still reduced by approximately 53%.

In the Phase III studies, following four doses of Leqvio at Day 1, Day 90 (~3 months), Day 270 (~6 months) and Day 450 (~12 months), LDL-C, total cholesterol, apolipoprotein B (Apo B), non-high-density lipoprotein cholesterol (non-HDL-C), and lipoprotein(a) (Lp(a)) were reduced.

Cardiac Electrophysiology

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

Pharmacokinetics (PK)

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 of inclisiran, plasma concentrations reached peak in approximately 4 hours post-dose with a mean C_{max} of 509 ng/mL. Concentrations reached undetectable levels after 24 to 48 hours post-dosing. The mean area under the plasma concentration-time curve from dosing extrapolated to infinity was 7980 ng*h/mL. Minimal to no accumulation of inclisiran in plasma was observed after repeat dosing.

Distribution

Inclisiran is 87% protein bound *in vitro* at the relevant clinical plasma concentrations. Following a single subcutaneous 284 mg dose of inclisiran to healthy adults, the apparent volume of distribution is approximately 500 L. Inclisiran has been shown to have high uptake into, and selectivity for the liver, the target organ for cholesterol-lowering.

Biotransformation/metabolism

Inclisiran is primarily metabolized by nucleases to shorter inactive nucleotides of varying length. Inclisiran is not a substrate for CYP450 or transporters.

Elimination

The terminal elimination half-life of inclisiran is approximately 9 hours, and no accumulation occurs with multiple dosing. Sixteen percent (16%) of inclisiran is cleared through the kidney.

Linearity/non-linearity

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

In the Phase I clinical study, a dissociation was observed between inclisiran pharmacokinetic parameters and LDL-C pharmacodynamic effects. Selective delivery of inclisiran to hepatocytes, where it is incorporated into the RNA-induced silencing complex (RISC), results in a long duration of action, beyond that anticipated based on the plasma elimination half-life of 9 hours. The maximal effects of reducing LDL-C were observed with a 284 mg dose, with higher doses not producing greater effects.

In Vitro evaluation of drug interaction potential

No formal clinical drug interaction studies have been performed. Inclisiran is not a substrate, inhibitor or inducer of CYP450 enzymes or transporters and is not expected to cause drug-drug interactions, or to be affected by inhibitors or inducers of CYP450 enzymes or transporters. In a population pharmacokinetic analysis, concomitant use of inclisiran had no meaningful impact on atorvastatin or rosuvastatin concentrations.

Special populations

A population pharmacodynamic analysis was conducted on data from 4,328 patients. Age, body weight and gender did not significantly influence inclisiran pharmacodynamics. No dose adjustments are recommended for these demographics.

Renal impairment

Pharmacokinetic analysis of data from a dedicated renal impairment study reported an increase in inclisiran C_{max} of approximately 2.3-, 2.0- and 3.3-fold, and an increase in inclisiran AUC of approximately 1.6-, 1.8- and 2.3-fold, in patients with mild, moderate and severe renal impairment relative to patients with normal renal function. Despite the higher transient plasma exposures over 24-48 hours, the reduction in LDL-C was similar across all groups of renal function. Based on population pharmacodynamic modeling, no dose adjustment is necessary in patients with end-stage renal disease. Based on PK, PD and safety assessments, no dose adjustment is recommended in patients with renal impairment (mild, moderate, or severe). The effect of hemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, hemodialysis should not be performed for at least 72 hours after Leqvio dosing.

Hepatic impairment

Pharmacokinetic analysis of data from a dedicated hepatic impairment study reported an increase in inclisiran C_{max} of approximately 1.1- and 2.1-fold, and an increase in inclisiran AUC of approximately 1.3- and 2.0-fold, in patients with mild and moderate hepatic impairment relative to patients with normal hepatic function. Despite the higher transient inclisiran plasma exposures, the reduction in LDL-C was similar between the groups of patients administered inclisiran with normal hepatic function and mild hepatic impairment. In patients with moderate hepatic impairment, baseline PCSK9 levels were markedly lower and the reduction in LDL-C was less than that observed in patients with normal hepatic function. No dose adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). Leqvio has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

12 Clinical studies

The safety and efficacy of Leqvio was evaluated in three 18-month, Phase III, randomized, double-blind, placebo-controlled trials in patients with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalents, or heterozygous familial hypercholesterolemia (HeFH).

Patients were taking a maximally tolerated dose of statins with or without other lipid-modifying therapy (such as ezetimibe), and required additional LDL-C reduction. Approximately 17% of patients were statin-intolerant. Patients were administered subcutaneous injections of 284 mg of Leqvio or placebo on Day 1, Day 90 (~3 months), Day 270 (~9 months) and Day 450 (~15 months). Patients were followed until Day 540 (~18 months).

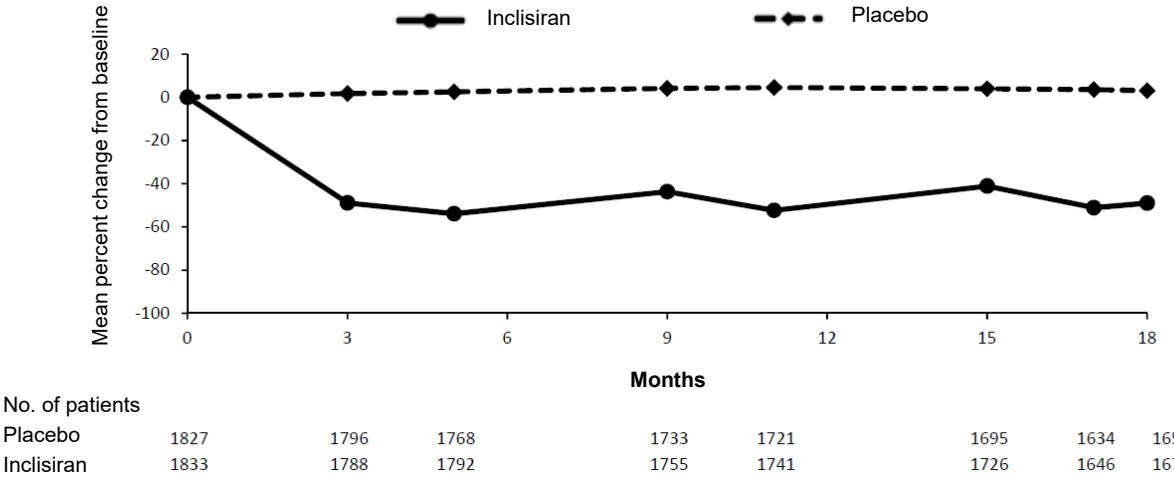
Phase III Pooled Analysis

In the Phase III pooled analysis, Leqvio administered subcutaneously lowered LDL-C between 50% and 55% as early as Day 90 (Figure 12-1), 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 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, race, gender, region, body mass index, National Cholesterol Education Program risk, current smoking status, baseline coronary heart disease (CHD) risk factors, family history of premature CHD, glucose tolerance status (i.e. diabetes mellitus type 2, metabolic syndrome, or neither), hypertension, and baseline triglycerides.

Inclisiran also reduced non-HDL-C, Apo B, total cholesterol, and Lp(a) in patients with primary hypercholesterolemia and mixed dyslipidemia. There were no clinically significant changes in high-density lipoprotein cholesterol (HDL-C) and triglycerides.

Figure 12-1 Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia treated with inclisiran compared to placebo (pooled analysis)



Primary hyperlipidemia in patients with clinical atherosclerotic cardiovascular disease

Two studies were conducted in patients with ASCVD and ASCVD Risk Equivalents (ORION-10 and ORION-11).

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 included the individual responsiveness to Leqvio, and the proportion of patients attaining global lipid targets for their level of ASCVD risk.

ORION-10 was a multicenter, double-blind, randomized, placebo-controlled 18-month trial conducted in 1,561 patients with ASCVD. Patients were taking a maximally tolerated dose of statins with or without other lipid modifying therapy, such as ezetimibe, and required additional LDL-C reduction. Patients were administered subcutaneous injections of 284 mg of Leqvio or placebo on Day 1, Day 90 (~3 months), Day 270 (~9 months) and Day 450 (~15 months).

The mean age at baseline was 66 years (range: 35 to 90 years), 60% were ≥65 years old, 31% were women, 86% were White, 13% were Black, 1% were Asian, and 14% identified as Hispanic or Latino ethnicity. The mean baseline LDL-C was 2.7 mmol/L (105 mg/dL). Sixty-nine percent (69%) 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 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 12-1 and Figure 12-2).

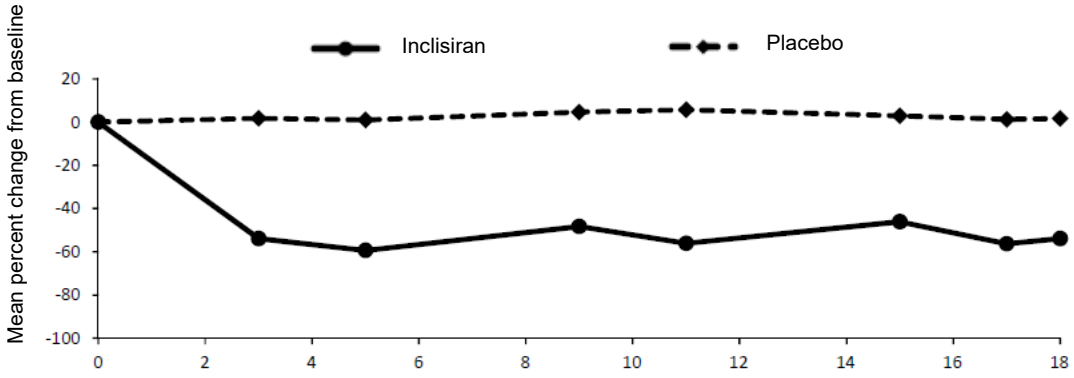
Leqvio also significantly reduced the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 by 54% compared to placebo (95% CI: -56%, -51%; p<0.0001). For additional results, see Table 12-1.

Table 12-1 Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in ORION-10

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	Apo B	Lp(a)*
Day 510 (mean percentage change from baseline)					
Placebo (n=780)	1	0	0	-2	4
Inclisiran (n=781)	-51	-34	-47	-45	-22
Difference from placebo (LS Mean) (95% CI)	-52 (-56, -49)	-33 (-35, -31)	-47 (-50, -44)	-43 (-46, -41)	-26 (-29, -22)

Apo B = Apolipoprotein B; CI = Confidence interval; LDL-C = Low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); LS = Least squares; Non-HDL-C = Non-high-density lipoprotein cholesterol.
*At Day 540; median percentage change in Lp(a) values.

Figure 12-2 Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia and ASCVD treated with inclisiran compared to placebo in ORION-10



ORION-10

No. of patients								
Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

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.

ORION-11 was an international, multicenter, double-blind, randomized, placebo-controlled 18-month trial which evaluated 1,617 patients with ASCVD or ASCVD risk equivalents (ASCVD risk equivalent was defined as those patients with type 2 diabetes mellitus, familial hypercholesterolemia, or 10-year risk of 20% or greater of having 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% were

ASCVD risk equivalent. Patients were taking a maximally tolerated dose of statins with or without other lipid modifying therapy, such as ezetimibe, and required additional LDL-C reduction. Patients were administered subcutaneous injections of 284 mg of Leqvio or placebo on Day 1, Day 90 (~3 months), Day 270 (~9 months) and Day 450 (~15 months).

The mean age at baseline was 65 years (range: 20 to 88 years), 55% were ≥65 years old, 28% were women, 98% were White, 1% were Black, 1% were Asian, and 1% were Hispanic or Latino ethnicity. The mean baseline LDL-C was 2.7 mmol/L (105 mg/dL). Seventy-eight percent (78%) 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.

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 12-2 and Figure 12-3).

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 12-2.

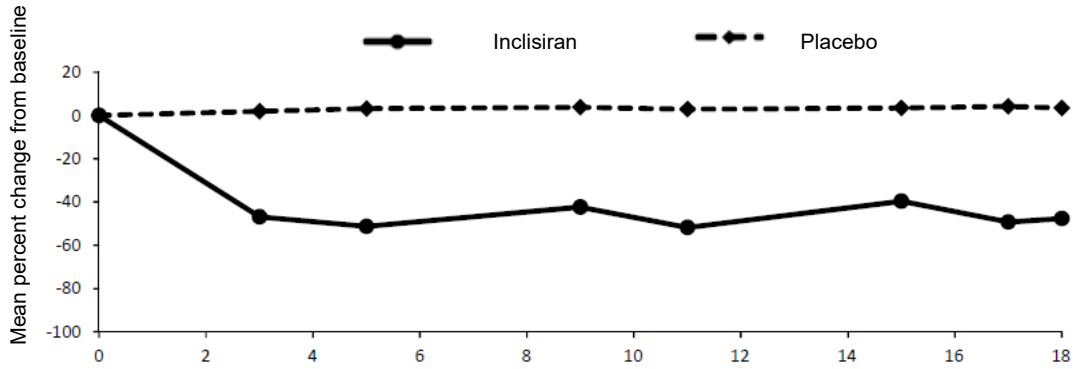
Table 12-2 Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in ORION-11

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	Apo B	Lp(a)*
Day 510 (mean percentage change from baseline)					
Placebo (n=807)	4	2	2	1	0
Inclisiran (n=810)	-46	-28	-41	-38	-19
Difference from placebo (LS Mean) (95% CI)	-50 (-53, -47)	-30 (-32, -28)	-43 (-46, -41)	-39 (-41, -37)	-19 (-21, -16)

Apo B = Apolipoprotein B; CI = Confidence interval; LDL-C = Low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); LS = Least squares; Non-HDL-C = Non-high-density lipoprotein cholesterol.

*At Day 540; median percentage change in Lp(a) values.

Figure 12-3 **Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia and ASCVD / ASCVD risk equivalents treated with inclisiran compared to placebo in ORION-11**

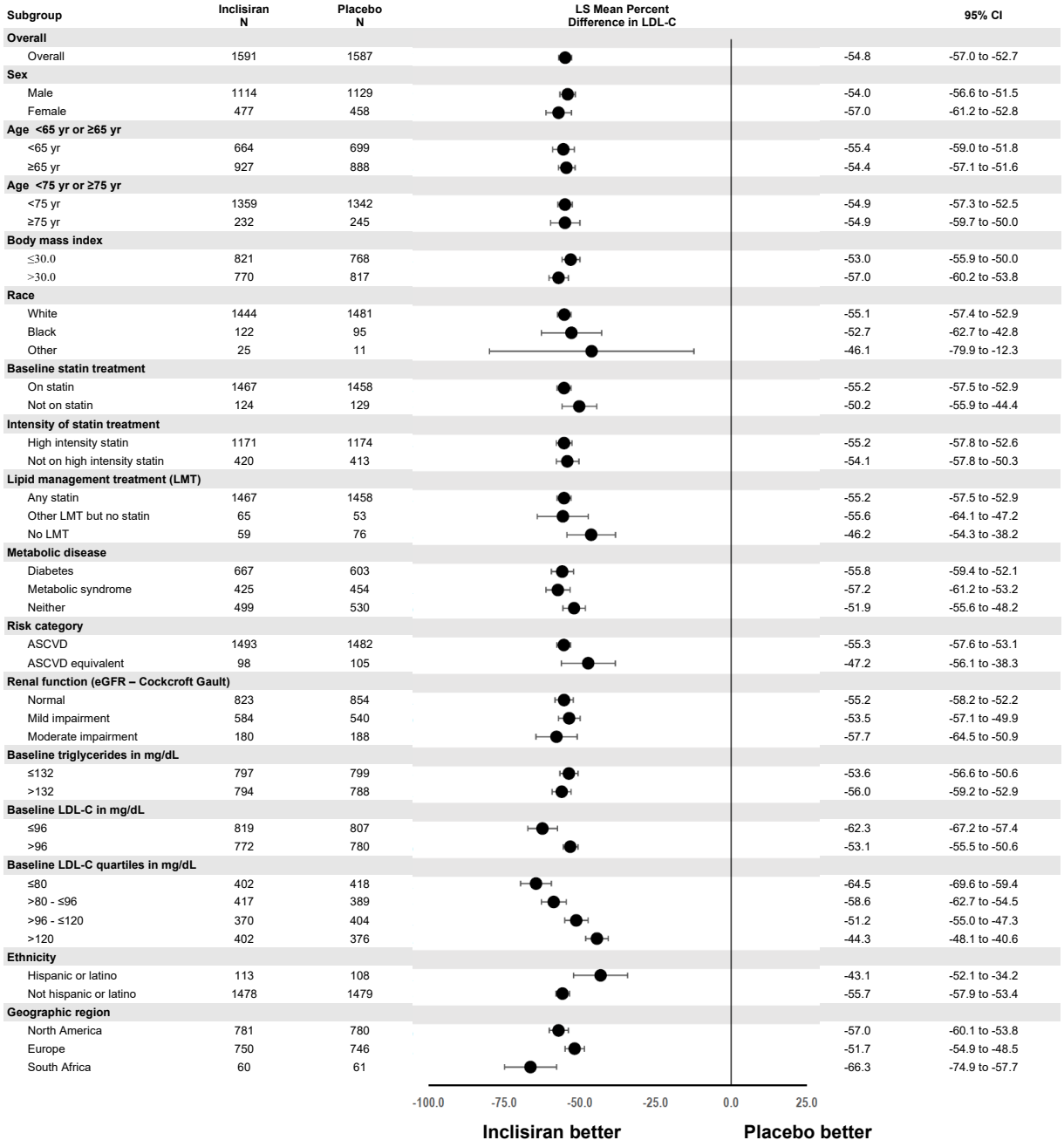


ORION-11								
No. of patients								
Placebo	807	797	785	774	773	764	739	749
Inclisiran	810	790	796	778	773	768	724	742

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.

In a pooled analysis of the two ASCVD studies (ORION-10 and -11), consistent and statistically significant ($p<0.05$) 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. This was observed across all subgroups irrespective of baseline demographics, baseline disease characteristics (including gender, age, body mass index, race and baseline statin use), comorbidities, and geographic regions (Figure 12-4).

Figure 12-4 Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510: Pooled analysis of ORION-10 and ORION-11



Heterozygous Familial Hypercholesterolemia (HeFH)

ORION-9 was an international, multicenter, double-blind, randomized, placebo-controlled 18-month trial in 482 patients with heterozygous familial hypercholesterolemia (HeFH). All patients had HeFH, were taking maximally tolerated doses of statins 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 clinical criteria ("definite FH" using either the Simon Broome or WHO/Dutch Lipid Network criteria).

The co-primary endpoints were the percentage change in LDL-C from baseline to Day 510 (~17 months) relative to placebo, and the time-adjusted percentage change in LDL-C from baseline after Day 90 (~3 months) and up to Day 540 (~18 months) 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 included the individual responsiveness to Leqvio, and the proportion of patients attaining global lipid targets for their level of ASCVD risk.

The mean age at baseline was 55 years (range: 21 to 80 years), 22% were ≥65 years old, 53% were women, 94% were White, 3% were Black, 3% were Asian, and 3% were Hispanic or Latino ethnicity. The mean baseline LDL-C was 4.0 mmol/L (153 mg/dL). Seventy-four percent (74%) were taking high-intensity statins, 15% were taking medium-intensity statins, and 10% were not on a statin. Fifty-two percent (52%) of patients were treated with ezetimibe. The most commonly administered statins were atorvastatin and rosuvastatin.

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 12-3 and Figure 12-5).

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 12-3.

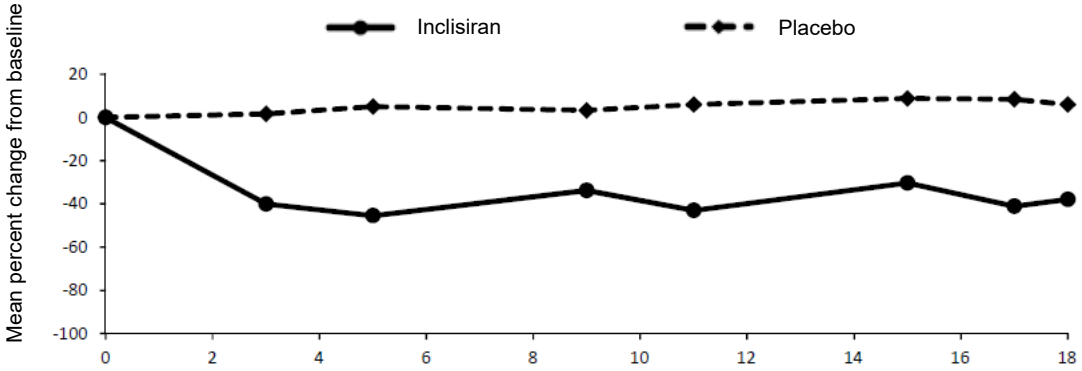
Table 12-3 Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in patients with HeFH in ORION-9

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	Apo B	Lp(a)*
Day 510 (mean percentage change from baseline)					
Placebo (n=240)	8	7	7	3	4
Inclisiran (n=242)	-40	-25	-35	-33	-13
Difference from placebo (LS Mean) (95% CI)	-48 (-54, -42)	-32 (-36, -28)	-42 (-47, -37)	-36 (-40, -32)	-17 (-22, -12)

Apo B = Apolipoprotein B; CI = Confidence interval; LDL-C = Low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); LS = Least squares; Non-HDL-C = Non-high-density lipoprotein cholesterol.

*At Day 540; median percentage change in Lp(a) values.

Figure 12-5 Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia and heterozygous familial hypercholesterolemia treated with inclisiran compared to placebo in ORION-9



ORION-9								
No. of patients								
Placebo	240	237	238	235	233	233	229	232
Inclisiran	242	240	239	240	237	237	231	232

At Day 510, the LDL-C target of <1.8 mmol/L (70 mg/dL) was achieved by 53% of Leqvio -treated patients with ASCVD compared to 1% 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 67% of Leqvio -treated patients compared to 9% of placebo-treated patients.

Consistent and statistically significant ($p<0.05$) 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, race and baseline statin use), comorbidities, and geographic regions.

13 Non-clinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and carcinogenic potential.

Repeat dose toxicity

In repeat dose toxicology studies conducted in rats and monkeys, the no observed adverse effect levels (NOAEL) were identified as the highest doses of inclisiran administered subcutaneously (250 mg/kg and 300 mg/kg, respectively) and were associated with safety margins of 54.9-fold in rats and 112-fold in monkeys, based on AUC, compared to exposures observed at the MRHD.

Carcinogenicity and mutagenicity

The carcinogenic potential of inclisiran was evaluated in a 6-month study in TgRasH2 mice and a 2-year study in Sprague-Dawley rats. Male and female TgRasH2 mice were administered inclisiran by subcutaneous injection once every 28 days at 300, 600 and 1500 mg/kg. Male and female Sprague-Dawley rats were administered inclisiran by subcutaneous injection once every

28 days at 40, 95 and 250 mg/kg. Inclisiran was not carcinogenic up to the highest doses tested, corresponding to safety margins of 256-fold in mice and 60.7-fold in rats, based on AUC, compared to exposures observed at the MRHD.

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

Reproductive toxicity

In a male fertility study, inclisiran was administered to male Sprague-Dawley rats by subcutaneous injection at 10, 50 and 250 mg/kg once every two weeks prior to and through mating. Inclisiran was not associated with paternal toxicity or effects on spermatogenesis, fertility or early embryonic development. The highest dose tested was associated with a safety margin of 44.1-fold based on AUC, compared to exposures observed at the MRHD.

In a female fertility study, inclisiran was administered to female Sprague-Dawley rats by subcutaneous injection at 10, 50 and 250 mg/kg once every four days prior to and through mating, and then once daily during the gestation period up to Day 7 post coitum. The high dose administered prior to gestation, 250 mg/kg, was reduced to 150 mg/kg for daily administration during gestation. Inclisiran did not produce maternal toxicity or have adverse effects on female fertility or early embryonic development. The highest dose tested was associated with a safety margin of 20.4-fold based on AUC, compared to exposures observed at the MRHD.

14 Pharmaceutical information

Incompatibilities

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

Special precautions for storage

This medicinal product does not require any special storage conditions.

Information might differ in some countries.

Leqvio must be kept out of the reach and sight of children.

Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufacturer

See folding box.

Package leaflet

Information issued: Apr 2020, corr Dec 2020.SIN

Novartis Pharma AG, Basel, Switzerland