Date: 13 September 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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: approved on 09.09.2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be 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
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
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
Em_{ax}	Maximum effect
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
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 nonproprietary name
ITT	Intention-to-treat
LMT	Lipid-modifying therapy
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)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance inclisiran of the medicinal product mentioned above. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

2.2 Indication and Dosage

2.2.1 Requested Indication

Inclisiran is intended for use in adults with hypercholesterolaemia (including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia, as an adjunct to diet:
- in combination with a statin or a statin with other lipid-lowering therapies in patients who require additional low-density lipoprotein (LDL-C) lowering 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 statins are contraindicated.

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:
- in combination with a maximum 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.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
The recommended dose of Leqvio is 284 mg given as a single subcutaneous injection: initially, again after 3 months and then every 6 months.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	18 May 2020
Formal control completed	25 May 2020
List of Questions (LoQ)	1 September 2020
Answers to LoQ	29 October 2020
Predecision	11 June 2021
Answers to Predecision	8 July 2021
Final Decision	9 September 2021
Decision	approval

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3 Medical Context

Lipid disorders can manifest as various diseases and lead to extensive alterations in plasma lipoprotein composition and function. Lipid disorders are often classified according to changes in laboratory values. Lipid disorders can also be caused by other diseases such as diabetes mellitus, thyroid disease, or nephrotic syndrome.

In most cases, lipid disorders imply hypercholesterolaemia. Epidemiological evidence shows a positive correlation and causal relationship between serum low-density lipoprotein cholesterol (LDL-C) and risk of coronary heart disease (CHD). Other clinical manifestations of atherosclerosis such as cerebrovascular disease (e.g. stroke) or peripheral arterial disease also appear to be related to serum LDL-C levels. Clinical trials with the LDL-C-lowering therapies of HMG-Co-A reductase inhibitors have demonstrated a reduction in CHD risk. The association between LDL-C levels and CHD risk has been demonstrated among different LDL-C levels. Epidemiological data indicate a continuous increase in risk of CHD from very low to "normal" and high LDL-C.

Elevated low-density lipoprotein cholesterol (LDL-C) is an important modifiable risk factor for the development of cardiovascular disease (CVD). LDL-C is a validated surrogate endpoint for cardiovascular risk reduction. Prevention interventions are considered the most sustainable solution to mitigate cardiovascular risk. Interventions that resulted in LDL-C control in patients with elevated LDL-C and in those at high cardiovascular risk have reduced the risk of cardiovascular events in these patient populations. Available therapies, such as statins and other lipid-lowering therapies, are effective but in some cases insufficient or intolerable to reduce LDL-C sufficiently. Thus, there remains a high unmet medical need.

The causal effect of LDL-C elevation and the increase in CHD risk is generally accepted by the scientific community. LDL-C lowering has been accepted by regulatory authorities as a surrogate parameter and has become the basis for approval of lipid-lowering therapies. It has also been generally accepted that LDL-C lowering <70 mg/dl might have a beneficial effect on CHD risk, but clinical outcome trial data with LDL-C lowering <70 mg/dl are limited.

4 Quality Aspects

4.1 Drug Substance

INN:	Inclisiran
Chemical name:	Sense strand: (2*S*,4*R*)-1-{1-[(2-acetamido-2-deoxy-β-D-galactopyranosyl)oxy]-16,16-bis({3-[(3-{5-[(2-acetamido-2-deoxy-β-D-galactopyranosyl)oxy]pentanamido} propyl)amino]-3-oxopropoxy}methyl)-5,11,18-trioxo-14- oxa-6,10,17-triazanonacosan-29-oyl}-4-hydroxypyrrolidin-2-yl]methyl hydrogen *all-P-ambo*-2'-O-methyl-*P*-thiocytidylyl-(3'→5')-2'-O-methyl-*P*-thiouridylyl-(3'→5')-2'-O-methyladenylyl-(3'→5')-2'-O-methylguanylyl-(3'→5')-2'-O-methyladenylyl-(3'→5')-2'-O-methylcytidylyl-(3'→5')-2'- deoxy-2'-fluorocytidylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-deoxy-2'-fluoroguanylyl-(3'→5')-2'-O-methyluridylyl- (3'→5')-thymidylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methylguanylyl-(3'→5')-2'-O-methylcytidylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methylguanylyl-(3'→5')-2'-O-methyl-3'-uridylate Antisense strand: *all-P-ambo*-2'-O-methyl-*P*-thioadenylyl-(5'→3')-2'-O-methyl-*P*-thioadenylyl-(5'→3')- 2'-O-methylguanylyl-(5'→3')-2'-O-methyladenylyl-(5'→3')- 2'-O-

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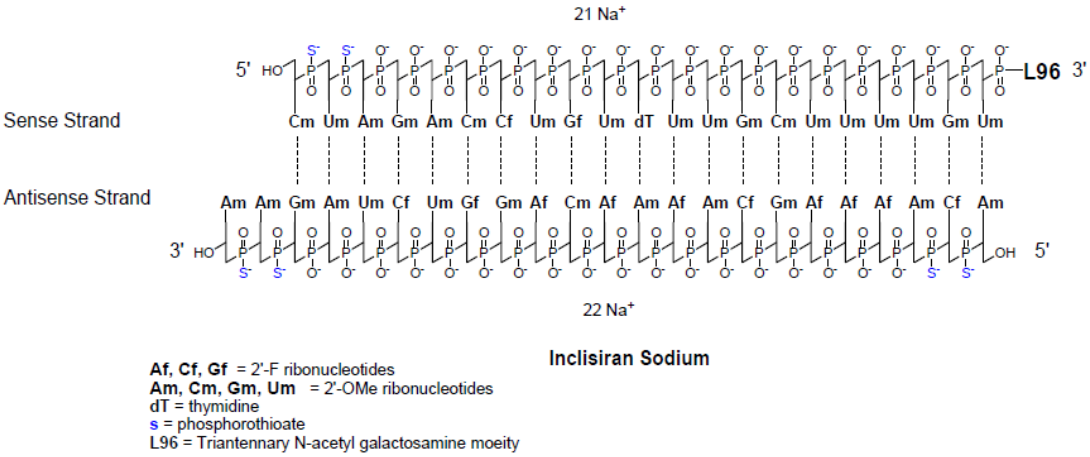
methyluridylyl-(5'→3')-2'-deoxy-2'-fluorocytidylyl-(5'→3')-2'-O-methyluridylyl-(5'→3')-2'-deoxy-2'-fluoroguanylyl-(5'→3')-2'-O-methylguanylyl-(5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')-2'-O-methylcytidylyl- (5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')-2'-O-methyladenylyl-(5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')- 2'-O-methyladenylyl-(5'→3')-2'-deoxy-2'-fluorocytidylyl- (5'→3')-2'-O-methylguanylyl-(5'→3')-2'-deoxy2'-fluoroadenylyl-(5'→3')-2'-deoxy-2'-fluoroadenylyl- (5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')-2'-O-methyl-*P*-thioadenylyl-(5'→3')-2'-deoxy-2'-fluoro-*P*-thiocytidylyl-(5'→3')-2'-O-methyladenosine

Molecular formula: C529 H664 F12 N176 Na43 O316 P43 S6

Molecular mass: 17,284.72 g/mol

Molecular structure:



Inclisiran Sodium

Af, Cf, Gf = 2'-F ribonucleotides
Am, Cm, Gm, Um = 2'-OMe ribonucleotides
dT = thymidine
s = phosphorothioate
L96 = Triantennary N-acetyl galactosamine moeity

Physicochemical properties:
Inclisiran sodium is a white to pale yellow powder. Inclisiran contains several stereogenic centres.

Synthesis:
The drug substance is manufactured by multiple step chemical synthesis. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification:
In order to ensure a consistent quality of inclisiran sodium, the specifications include all relevant test parameters.

Stability:
The bulk drug substance is packaged in HDPE bottles. Appropriate stability data have been presented.
Based on the results, a satisfactory retest period was established.

4.2 Drug Product

Description and composition:
Inclisiran injection drug product is a sterile solution in a prefilled syringe (PFS). The solution is colourless to pale yellow.

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Component, grade	Concentration (mg/mL)	Amount Per PFS	Function
Inclisiran Sodium*, In House	200	300 mg**	Drug Substance
(*corresponding to Inclisiran)	189	284 mg	Drug Substance (free acid)
Water for Injection, USP, Ph. Eur.	N/A	q.s. to 1.5 mL	Diluent
Sodium Hydroxide, NF, Ph. Eur.	N/A.	q.s. to target pH 7.0	pH adjustment
Phosphoric Acid, NF, Ph. Eur.	N/A	q.s. to target pH 7.0	pH adjustment
Nitrogen, NF, Ph.Eur.	N/A	N/A	Head space gas

USP: United States Pharmacopeia
NF: National Formulary
Ph. Eur.: European Pharmacopeia
q.s.: quantum sufficit
**Sodium content per dose is ≤ 1 mmol (23 mg). There are 16 mg of sodium from the drug substance and less than 0.1 mg from the sodium hydroxide solution for pH adjustment in each PFS.

Manufacture:
The drug substance is dissolved in water for injection, and the pH is adjusted to 7.0. The product is then passed through a sterilising filter and filled aseptically into syringes.

Specifications:
Release specifications have been defined based on the characteristics of the drug substance and the results of the stability studies in order to ensure a consistent quality.

Container-closure system:
Inclisiran solution for injection is packaged in a prefilled syringe system inerted with nitrogen.

Stability:
The product is stable for 36 months below 25°C, as demonstrated by the stability studies.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

5.1 Pharmacology

Pharmacodynamics
Inclisiran is a chemically synthesised small-interfering RNA (siRNA) molecule, composed of an antisense strand (AS) which is directed against the human Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) mRNA, and a sense strand (S) conjugated with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. Expression of PSCK9 protein in the liver is crucial for the down regulation of low-density lipoprotein (LDL) receptor expression. Inclisiran utilises the RNA interference mechanism to drive the catalytic breakdown of PCSK9 mRNA. This results in increased LDL receptor recycling and increased expression on the hepatocyte surface, which is paralleled by an increase in LDL uptake.

Transfection of HeLa or Hep3B cells with inclisiran inhibited PCSK9 expression with an IC_{50} value in the picomolar range. Due to the 100% sequence homology between the inclisiran target human and cynomolgus monkeys PCSK9, the *in vivo* pharmacological activity of inclisiran was primarily investigated in cynomolgus monkeys.

A dose-dependent decrease in PCSK9 protein and LDL-C levels was observed following single-dose subcutaneous (SC) administration of inclisiran in monkeys. A temporal disconnection between inclisiran plasma exposure and pharmacodynamic (PD) effects was confirmed in several studies, demonstrating a sustained PSCK9 protein reduction for up to 100 days post administration, albeit with undetectable inclisiran plasma levels within 24 hours. Different repeat-dose regimens led to comparable long-lasting steady-state reductions in PCSK9 and LDL-C with similar kinetics.

Whereas no PD effect was observed at 0.1 and 0.3 mg/kg bw in female cynomolgus monkeys, a marked effect on PCSK9 and LDL-C was found at 3 and 6 mg/kg bw. There was a dose-dependent effect on the duration of PCSK9 and LDL-C to reach the baseline (up to day 180 post dose in the 10 mg/kg bw dose group). The pharmacological effects of inclisiran were investigated in an SC multi-dose regimen following an initial 6 mg/kg bw administration in cynomolgus monkeys. It was demonstrated that monthly administration of 1mg/kg bw or higher, subsequent to an initial dose of 6 mg/kg bw, was able to maintain PCSK9 and LDL-C reductions for up to 1 year. In contrast, partial recovery prior to the next dose was noted with an administration regimen composed of an initial administration of 10 mg/kg bw, followed by 10mg/kg bw every 3 months. In another female cynomolgus monkey study, PD and pharmacokinetics (PK) of inclisiran were investigated following single intravenous (IV) and single SC or multiple-dose SC administration regimens. Steady-state PCSK9 reductions were noted after the last dose for every administration regimen for up to 84 days following both the single SC dose and in the multiple SC dose regimens. LDL-C reduction below 50% of baseline for 56 days was observed in the biweekly multiple dose administration regimen.

The off-target activity of inclisiran was evaluated primarily *in silico*. A sequence homology approach was followed to evaluate the AS activity of inclisiran on potential off-target transcripts. Parent and chain-shortened metabolites of inclisiran were searched against the human transcriptome. A weighted brute force algorithm, enhancing the weight of the ‘seed’ region of inclisiran with respect to the interfering machinery of the RNA-induced silencing complex (RISC) associated with argonaute RISC Catalytic Component 2 (Ago2) was applied. Twenty potential off-targets were selected, and 18 that were expressed in Hep3b cells transfected by inclisiran were quantified by quantitative PCR. Taking into account a ≥ 45-fold factor between the on-target inhibition of PCSK9 and potential off-target inhibition, none of the tested transcripts was inhibited. No data were provided for the inhibition potential of transcripts by the S strand of inclisiran. The applicant explained that the extensive 2’-O-methyl modifications and the addition of the GalNAc ligands to the S strand of inclisiran significantly decrease the potential inhibition of off-target transcripts. This rationale was substantiated with the absence of overt toxicities in long-term toxicology studies.

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A respiratory and cardiovascular safety pharmacology study was carried out in male cynomolgus monkeys. Conventional safety parameters were recorded, and no inclisiran-related effects were observed on the heart parameters (heart rate, systolic, diastolic, and mean arterial pressures, pulse pressure, PR, QT, QTc interval, or QRS duration). Arrhythmias observed during the dosing phase were not attributed to inclisiran and showed neither dose- nor time-dependence. There were no inclisiran effects on the respiratory rate. CNS parameters, including postural reactions, spinal nerve function, and cranial nerve effects, were included in the repeated-dose toxicological studies conducted in cynomolgus monkeys. No neurobehavioural findings related to inclisiran were observed. Whereas no dedicated PD drug interaction studies have been performed, effects of the co-administration of inclisiran and atorvastatin on PSCK9 and LDL-C levels were investigated in a 13-week repeated-dose toxicology study. The combination of inclisiran and atorvastatin did not result in any extensive variations in PD parameters as compared to single compound administration.

5.2 Pharmacokinetics

The pivotal PK studies were conducted in Sprague-Dawley rats and cynomolgus monkeys following single IV, and single and multiple SC dose administration. PK parameters, bioavailability, tissue distribution, metabolism, and excretion were evaluated with inclisiran. Additionally, ^{14}C-radiolabelled inclisiran was utilised for more comprehensive metabolism and distribution analysis. The validation of the analytical methods to evaluate the PK of inclisiran and its metabolites included linearity, sensitivity, accuracy, precision, dilution, selectivity, recovery, matrix effect, and carryover. Notably, the incurred sample reanalysis was carried out in 2 studies [8302576; 8302575], and the standard curve of the LC-TOF-MS assay was based on the duplex of the calibration curves of the AS and sense strands.

The absolute SC bioavailability of inclisiran was 48.9% and 29.3% in rats and monkeys, respectively. The prolonged half-life of inclisiran at the injection site (approximatively 526 hours in rats), coupled with the high recovery of radiolabelled inclisiran in the rat carcasses (approximatively 80%), may explain the effective systemic absorption and the seemingly low bioavailability (via the SC route). Following SC administration in both species, plasma C_{max} and AUC_{0-t} of inclisiran exhibited an approximate dose-relationship exposure with no gender differences. In monkeys, the T_{max} and the elimination half-life were approximately 2 hours and ranged from 2.2 to 4.3 hours, respectively. There is an inversely dose-proportional binding of inclisiran to plasma protein (ranging from 87.4% to 93.1% for the lowest inclisiran concentration of 0.5 µg/mL). Tissue distribution investigations with radiolabelled inclisiran revealed high levels of radioactivity in the liver, in the kidneys and at the injection site (SC administration). The lymph nodes also showed high levels of radioactivity, but to a lesser extent as compared to the aforementioned organs. In contrast, very low levels of radiolabelled inclisiran were found in neurological tissues. Although the long retention time of inclisiran precluded the determination of the half-life for all analysed tissues, the estimated liver half-lives were 1980 and 271 hours for rats and monkeys, respectively. In monkeys, an estimated kidney half-life of about 10,000 hours was calculated.

The degree of inclisiran metabolism was investigated in serum from different species with and without human liver S9 fractions. When incubated with mouse, rat, monkey, and human serum for 24 hours with liver S9-fractions, inclisiran showed sequence integrity for the AS strand ranging from 41% to 85% (72% to 85% without S9) and, for the S strand, ranging from 64% to 94% (87% to 95% without S9). Metabolites formed primarily by sequential exonuclease on the 5' and 3' ends, likely due to the enhanced stability of backbone of inclisiran. Although, AS metabolic investigations with various matrices identified 18 AS and 35 AS metabolites in rats and monkeys, respectively, only the AS(n-1) metabolite was consistently quantified in all matrices. The number of S strand metabolites identified was 20 in monkeys and 12 in rats, with metabolites predominantly characterised by the removal of the GalNAc groups and their associated linkers.

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Inclisiran is primarily excreted by kidneys, exhibiting recovery rates (over a 7-day period) of approximately 29% and 32% in the urine of rats and monkeys, respectively. Approximately 39% of radiolabelled inclisiran was recovered in the carcasses of rats (after 96 hours). This correlates with the long retention time of inclisiran in tissues. Drug-drug interaction with inclisiran is not likely. No significant direct or time-dependent inhibitory activity of inclisiran was observed against 7 human cytochrome P450 isoforms. Moreover, inclisiran does not function as a substrate or inhibitor of major human transporter proteins.

5.3 Toxicology

Toxicity

No single-dose toxicity studies were conducted. Since findings related to single-dose toxicity studies can be obtained with other studies, this is considered acceptable. In repeated-dose toxicity studies, no overt toxicity was noted. The major findings were related to the marked changes in the lipid profile, which are most likely linked to the PD activity of inclisiran and to some effects predominantly localised in the liver and the kidneys in rats, and in the liver and lymph nodes in monkeys. In the rat 4-, 15-, and 29-week studies, microscopic findings of hepatocyte vacuolation (characterised as microvesicular and/or macrovesicular cytoplasmic vacuolation) were identified in male and/or female rats (in most dose groups). A notable reduction in hepatic vacuolation was observed at termination of the recovery period in all 3 studies, suggesting partial recovery. Basophilic granules in kidney tubules were noted in the 4-week rat study (in the 50 and 250 mg/kg dose groups), with evidence of partial recovery. In the 15- and 26-week rat studies, the basophilic granules in the kidney tubules noted at the end of treatment (at ≥25 mg/kg in the 15-week rat study and at ≥50 mg/kg in the 29-week rat study) were restricted solely to the 250 mg/kg dose group at the end of the recovery period. In the monkey 4-, 15-, and 29-week studies, no hepatocyte vacuolation was noted microscopically in the 4-week study, but microscopic basophilic granules in the hepatocyte cytoplasm were noted in the 15- and 40-week monkey studies for several animals across all dose groups. At the end of the recovery period in all 3 monkey studies, basophilic granules were noted in all groups in the 40-week study, with lower incidence and severity indicating partial recovery. Lymph node findings in the 3 monkey studies consisted of vacuolated macrophages characterised by accumulations of foamy cytoplasmic vacuoles, which were noted in all dose groups. At the end of the recovery period, a reduction in severity of macrophage vacuolation was observed, indicating partial recovery; in the 15-week study there was evidence of complete recovery/reversal in the 10 mg/kg dose group based on an absence of vacuolation and basophilic granules. None of the microscopic findings noted in the rat and monkey 4-, 15, and 40-week studies were considered adverse, due to lack of severity, evidence of recovery, and lack of correlation with clinical pathology parameters. Minimal increases in ALP and ALT were noted only in the highest dose group (250 mg/kg) in the 29-week rat study, and minimal/non-statistically significant increases in ALP only were noted in the 15- and 40-week monkey studies. These changes in ALP and ALT were not considered adverse, due to the small magnitude of change and the fact that they reversed by the end of the recovery period. No inclisiran-related changes in ECG parameters were noted during the 40-week monkey study, and there were no findings in neurobehavioural evaluations performed during the monkey repeat-dose studies. No alterations in the levels of G-CSF, IL-6, IP-10, KC, MCP-1, and TNF-α were noted. The T-cell dependent antibody response (TDAR) following immunisation with keyhole limpet haemocyanin (KLH) was not affected by inclisiran during the dosing or recovery periods. NOAELs were 250 mg/kg and 300 mg/kg in rats and monkeys, respectively, the highest doses tested in the conducted repeat-dose toxicology studies. As compared to the 300 mg human clinical dose, the C_{max}- and AUC_{0-t}-based safety margins are 101-fold and 99.6-fold for monkeys (99 and 48.9-fold for rats), respectively.

Bacterial Ames, *in vitro* chromosomal aberration (using human peripheral blood lymphocytes (HPBLs), and *in vivo* micronucleus assays were part of the genotoxicity battery of tests performed on inclisiran. Based on negative results in these 3 assays, inclisiran is not considered to be genotoxic. Long- and short-term carcinogenicity studies with inclisiran have been performed in rats and mice. In the 2-year rat carcinogenicity study, a significant increase in the rate of benign mammary

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fibroadenoma was observed in female rats in the 95 and 250 mg/kg dose groups, but not in the 40 mg/kg dose group. Since fibroadenomas are not considered premalignant in humans and the observed incidence of these tumours was similar to published background levels, these increases in fibroadenomas are not a concern to humans. In the TgRasH2 mouse study, there were no inclisiran-related effects on mortality or the incidence of clinically observed palpable masses, nor were any inclisiran-related macroscopic or microscopic findings detected. Overall, based on the results of the 2-year rat and 6-month transgenic mice carcinogenicity studies, inclisiran is not considered to be carcinogenic in mice and rats and does not indicate a carcinogenic potential in humans.

No inclisiran-related effects on paternal toxicity, fertility, spermatogenesis, or early embryonic development were noted in a 4-week reproduction toxicity study carried in rats with doses up to 250 mg/kg bw. Similarly, no maternal toxicity, female fertility, or early embryonic development impairments related to inclisiran were observed. Exposure margins were 19 times for male and female fertility and 37 times for embryo-foetal toxicity, based on the $AUC_{0\text{-}t}$ at the recommended therapeutic dose. No inclisiran-related effects were observed on the development of the F1 generation.

Toxicokinetic (TK) parameters were determined in rat and monkey studies. The relatively short plasma half-life of inclisiran, ranging from 1.8 to 16.5 hours in monkeys and from 0.76 to 7.65 hours in rats, was noted without gender differences. Some anti-drug antibody (ADA) events were detected at, or near, the end of the dosing periods in the 15-and 40-week toxicology studies carried out in monkeys. Limited comprehensive ADA data from TK studies do not allow any conclusions to be drawn on the ADA formation. However, no substantial neutralising effects were observed on PD or PK parameters.

A monkey study was performed to evaluate the potential for additional toxicity when inclisiran is combined with atorvastatin. When inclisiran (30, 100, or 300 mg/kg administered monthly) was combined with atorvastatin (administered daily), no additional toxicity events were observed as compared to treatment with either inclisiran or atorvastatin alone.

5.4 Nonclinical Conclusions

The noted persistent reduction in the lipid profile in the animal studies mimics the effects observed in clinical studies. The PK studies have demonstrated that the preferred target site of inclisiran, as expected by its design, is the liver. Toxicity studies do not reveal any overt toxicity. Non-advertent effects were mostly reversible. No reproductive toxicity has been observed. The combination of inclisiran with atorvastatin did not negatively affect the efficacy and safety profiles. The safety margins based on the NOAEL (which is the highest dose used in pivotal rat and monkey studies) were around 100-fold and 50-fold based on C_{max} and $AUC_{0\text{-}t}$, respectively. However, as siRNA is a new compound class, no long-term experience exists, and negative effects cannot be ruled out when it is used over a period of many years. Effects on the liver and kidney, on hormonal systems, especially steroid hormones, on haematology, on exposed organs other than liver and kidney, and unpredictable immune reactions should be monitored, especially after ADA development. Based on the aforementioned supporting non-clinical findings, it can be concluded that an unacceptable risk for inclisiran is not expected. From a non-clinical point of view inclisiran can be approved.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The pharmacokinetics and pharmacodynamics of inclisiran have been studied in healthy subjects and patients following subcutaneous (s.c.) administration in the dose range of 25 - 900 mg.

ADME

Absorption
Following subcutaneous administration of single doses in the range of 25 – 900 mg inclisiran, plasma concentrations of inclisiran increased rapidly, reaching maximum values within 0.5 – 12 h. The absolute bioavailability of inclisiran has not been determined.

Distribution
Inclisiran plasma protein binding in human plasma was inversely concentration-dependent: ~87% at 0.5 µg/ml and 17% at 50 µg/ml (C_{max} following 300 mg was 0.509 µg/ml). Following a single s.c. dose of 300 mg inclisiran, the mean apparent volume of distribution was 508 L. Distribution to body fluids other than plasma or urine has not been studied in humans.

Metabolism
No human ADME study using radioactively labelled inclisiran has been performed, which is acceptable in light of a very long tissue half-life observed in animal studies. *In vitro* and animal data indicated that inclisiran was primarily metabolised by exonucleases.

Excretion
Following a single s.c. dose of 300 mg inclisiran, the mean apparent plasma clearance of inclisiran was 38.1 L/h and the associated plasma half-life was 9.6 h. At the same dose, the mean fraction excreted in urine was 16%.

PK after multiple doses
Inclisiran did not accumulate in plasma following s.c. administration of multiple doses of inclisiran (125 mg QW, 250 mg Q2W, or 300 mg or 500 mg Q4W).

Dose-proportionality
AUC and C_{max} increased in a dose-proportional manner over the investigated dose range.

Special Populations / Intrinsic Factors

Hepatic impairment
Inclisiran exposure increased with decreasing hepatic function: in subjects with mild hepatic impairment (Child-Pugh A) inclisiran C_{max} was similar and AUC_{0-t} was increased by 30% while, in subjects with moderate hepatic impairment (Child-Pugh B), inclisiran C_{max} was increased by 110% (to 2.1-fold) and AUC_{0-t} by 100% (to 2.0-fold) compared to subjects with normal hepatic function.

The decrease in LDL-C and PCSK9 from baseline was comparable in subjects with mild hepatic impairment and normal hepatic function, but was less pronounced in subjects with moderate hepatic impairment: the extent of decrease was lower (LDL-C ~- 52% vs. - 40% change from baseline to day 60), the maximum reduction was reached later and the effect was shorter in subjects with moderate hepatic impairment.

These data suggest that patients with moderate hepatic impairment benefit less from treatment with inclisiran. The mechanistic explanation for these differences is still not well understood. However, the safety profile was acceptable, and there is no evidence of any liver toxicity. Therefore, no dose

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adjustment in patients with mild and moderate hepatic impairment is required, taking into account the fact that inclisiran is present in the plasma for only 24 to 48 hours every 6 months.
Inclisiran has not been studied in subjects with severe hepatic impairment.

Renal impairment
Inclisiran exposure (AUC_{0-t}) was increased by 60% (to 1.6-fold) in subjects with mild renal impairment, by 80% (to 1.8-fold) in subjects with moderate renal impairment, and by 130% (to 2.3-fold) in subjects with severe renal impairment.

While the LDL-C reduction was comparable, both in extent and over time, in subjects with normal renal function and subjects with moderately and severely impaired renal function, the extent of LDL-C reduction was less in subjects with mildly impaired renal function (max. reduction at day 60 of -35% vs. -58%).

As for hepatic impairment, these data suggest that patients with mild renal impairment benefit less from treatment with inclisiran. A mechanistic explanation for this difference in effect is not provided. However, the safety profile was acceptable, and there is no evidence of any renal toxicity. Therefore, no dose adjustment in patients with renal impairment is required, taking into account the fact that inclisiran is present in plasma for only 24 to 48 hours every 6 months.

Inclisiran was not studied in subjects with ESRD under dialysis.

Interactions
No dedicated clinical studies were performed to assess pharmacokinetic drug-drug interactions. This is acceptable, since *in vitro* studies indicated that inclisiran does not inhibit common CYPs and is neither a substrate nor an inhibitor of relevant drug transporters at clinically relevant concentrations.

Potential PK interactions of inclisiran on commonly coadministered statins (atorvastatin and rosuvastatin) have been assessed using a PopPK approach. While the applied PopPK models were assessed to be of limited value, because they did not describe the statin data well, a graphical comparison of the observed rosuvastatin and atorvastatin concentrations in the inclisiran versus placebo group indicated no major differences in statin concentrations.

Pharmacodynamics

Mechanism of action and primary pharmacology
Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA) that inhibits the production of proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 binds LDL-receptors on the surface of hepatocytes and thereby promotes degradation of LDL receptors. Since LDL-receptors are involved in clearing circulating LDL-C, the reduction of PCSK9 levels by inclisiran increases LDL receptor levels on the surface of hepatocytes and thereby promotes clearance of LDL-C from the circulation.

The effect of inclisiran on the levels of plasma PCSK9 and LDL-C was characterised in detail as part of all Phase 1 studies. A pronounced temporal disconnect between inclisiran plasma levels and the PD effects in plasma was observed. While inclisiran is detectable in plasma for a maximum of 48h post dose, the maximum PD effects are usually observed by day 30 post dose or even later. Therefore, the studies focused on the characterisation of the relationship between inclisiran dose and PD response, rather than the relationship between inclisiran exposure and response.

Overall, following single s.c. administration, reductions of plasma PCSK9 and LDL-C from baseline could be observed within 2-8 days post dose but the maximum reduction was obtained between day 30 and day 84 post dose. Plasma PCSK9 and LDL-C reductions were more pronounced with increasing doses up to 300 mg, where the maximum effect was reached.

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Besides a descriptive analysis of the relationship between the dose of inclisiran and PCSK9 and LDL-C levels, a PopPD model was developed and used to simulate the effects of delayed or missed doses.

The PopPD model structure reflected the mechanism of action of inclisiran. Inclisiran was directly administered into, and eliminated from, a hypothetical liver effect compartment, which in turn was linked to the zero-order synthesis rate for PCSK9 through an inhibitory E_{max} model. PCSK9 levels were then linked to the first-order degradation/clearance rate of LDL-C through the use of a second inhibitory E_{max} model. Various covariate effects were included in the model. However, among these, only baseline PCSK9 and LDL-C levels and disease status (HeFH vs. ASCVD) had relevant effects on LDL-C levels.

Overall, the model was considered suitable to be used for simulations with respect to delayed or missed doses. These simulations supported the dosing recommendations in case of delayed or missed dosing.

Secondary Pharmacology (Safety)
The potential of inclisiran to affect cardiac repolarisation was assessed in a thorough QT study, following administration of a single 900 mg s.c. dose, which is 3-fold the requested therapeutic dose. The study results indicated that inclisiran caused a maximum mean (90% CI) ddQTcF of 2.5 (0.6 – 4.5) msec at 4h post dose, which is below the threshold of regulatory concern of 10 msec.

6.2 Dose Finding and Dose Recommendation

In a placebo-controlled, double-blind, randomised Phase II study of 501 adult subjects with high cardiovascular risk (ASCVD) or high ASCVD-risk equivalents (e.g. diabetes and familial hypercholesterolaemia) and elevated LDL-C levels (despite the maximum tolerated dose of LDL-C-lowering therapies), inclisiran was injected subcutaneously to determine the optimal dose regimen (ORION-1). All subjects received a single dose of inclisiran or placebo on day 1. The single-dose groups (inclisiran sodium 200 mg, 300 mg, 500 mg, and 3 corresponding placebo groups) received no other study drug. The double-dose groups received a second dose of study drug on day 90.

Treatment with inclisiran resulted in significantly greater reductions in both LDL-C levels and PCSK9 levels at day 180 compared to placebo. The greatest reduction in LDL-C levels at day 180 was achieved with the 300 mg dose of inclisiran at day 1, followed by a second dose at day 90. In the double-dose inclisiran 300 mg group, every subject had a reduction in LDL-C levels, with a mean absolute reduction of 64.2 mg/dL at day 180. By day 360, inclisiran was well tolerated in all single- and double-dose groups. Based on these data, 300 mg as a double dose (day 1 and day 90) and every 6 months thereafter was selected as the dosing regimen for subsequent Phase III clinical trials. The 300 mg dosage was superior in efficacy to the 200 mg dosage, whereas no further benefit was apparent for the 500 mg dosage (single or double).

6.3 Efficacy

Primary Efficacy Endpoints

The primary efficacy endpoints were met with a high degree of consistency across the 3 confirmatory Phase III studies, ORION 9, ORION-10, and ORION-11, and also confirmed the corresponding estimates from the Phase II dose-finding study (ORION 1) and its extension study, ORION 3.

In the 482 patients with heterozygous familial hypercholesterolaemia (HeFH), treatment with inclisiran (300 mg SC on day 1, day 90, day 270, and day 450) showed a highly significant, 49.9% reduction in LDL-C from baseline at day 510 and an equally highly significant, approximately 44.3%, reduction in LDL-C between day 90 and day 540. The result is largely unchanged and robust, independently of

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sensitivity analyses and the analysis population used (ORION-9). In this study, all relevant secondary efficacy endpoints were also met at a highly significant level.

In the 1561 patients from 146 centres in the United States with atherosclerotic cardiovascular disease (ASCVD), treatment with inclisiran showed a highly significant, placebo-adjusted percentage LDL-C reduction from baseline to Day 510 of 57.6%, and an equally highly significant, 53.8% LDL-C decrease between Day 90 and Day 540 (ORION-10). All but 3 subjects (99.6%; 762/765) responded to inclisiran with a lowering of LDL-C; in these 3 subjects, there was a reduction in PCSK9 but not LDL-C. Inclisiran lowered PCSK9, total cholesterol, apo-B, Lp(a), and non-HDL-C, reflecting changes in LDL-C during the 18-month study period. The efficacy of inclisiran was consistent in all subgroups.

Among the 1617 patients from 64 centres in 7 European countries and 8 centres in South Africa with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents, there was a highly significant, placebo-adjusted percent LDL-C decrease from baseline to day 510 of 53.5%, and an equally highly significant, 49% LDL-C decrease between day 90 and day 540 (ORION-11). Most subjects (99.4%; 797/802) responded to inclisiran by demonstrating a decrease in LDL-C at any time during the study. Inclisiran lowered PCSK9, total cholesterol, apo-B, Lp(a), and non-HDL-C, reflecting changes in LDL-C during the 18-month study period. The efficacy of inclisiran was consistent in all subgroups.

Secondary Efficacy Endpoints

Inclisiran lowered total cholesterol, Apo B, and non-HDL-C compared with placebo, consistent with changes in LDL-C resulting from PCSK9 inhibition. Reductions in Lp(a) were also observed.

6.4 Safety

Overall safety database

In the Safety Pool, 3655 patients from the 3 confirmatory, randomised, double-blind, 18-month, placebo-controlled Phase III trials were included in the Safety Population: 481 patients with HeFH (ORION-9), 1559 patients with ASCVD (ORION-10), and 1615 patients with ASCVD or ASCVD-risk equivalents (ORION-11).

Adverse events
In the safety pool, the incidence of TEAEs, TESAEs, deaths, and study discontinuations due to TEAEs was similar between placebo-treated and inclisiran-treated patients. The most common TEAEs that occurred more frequently in inclisiran-treated patients were diabetes mellitus, nasopharyngitis, arthralgia, back pain, urinary tract infection, diarrhoea, bronchitis, cough, headache, angina, dizziness, pain in extremity, dyspnoea, and injection site reaction.

The incidence of death was 1.5% in patients treated with placebo and also 1.5% in patients treated with inclisiran. The most common cause of death was heart disease.

In the safety pool, there were no clinically significant changes in ALT, AST, total bilirubin, or ALP over the course of the studies in either placebo-treated or inclisiran-treated patients. There were no clinically significant changes in serum creatinine, BUN, or eGFR during the studies in either placebo-treated or inclisiran-treated patients. There were no imbalances in the number of patients with CS changes in serum creatinine between placebo and inclisiran.

Special safety aspects

At 8.2%, more inclisiran-treated patients reported an AE at the injection site than placebo-treated patients (1.8%). More inclisiran-treated patients (5.0%) than placebo-treated patients (0.7%) reported

clinically relevant injection site TEAEs (injection site erythema, injection site hypersensitivity, injection site pruritus, injection site rash, and injection site reaction). Except for TEAE at the injection site (more common in women and patients with a history of allergy), there were no clinically meaningful differences between inclisiran-treated patients compared with placebo-treated patients for any of the safety subgroups.

Long-term safety
There are 3 ongoing long-term safety studies. The ORION-3 study is an extension study of the ORION-1 dose-finding study for an additional 4 years. Preliminary interim results confirm the efficacy and safety results of the ORION-1 study. The study identified no new safety concerns. The ORION-8 study is a long-term extension study to the confirmatory Phase III ORION-9, ORION-10, and ORION-11 studies and is planned for an additional 3 years and 3,700 patients. The double-blind, randomised, placebo-controlled ORION-4 trial is a study of 15,000 ASCVD patients to assess cardiovascular outcomes (MACE) over a treatment period of 4-5 years. No results have been reported on these studies to date.

6.5 Final Clinical and Clinical Pharmacology Benefit-Risk Assessment

Increased low-density lipoprotein cholesterol (LDL-C) is an important modifiable risk factor for the development of cardiovascular disease (CVD). LDL-C is a validated surrogate endpoint for cardiovascular risk reduction and is accepted and confirmed by the guidelines for the development of medicinal products for the therapy of lipid diseases e.g. EMA/CHMP/ 748108/2013, Rev. 3. Evidence of LDL-C lowering as a therapeutic goal for cardiovascular event reduction comes from epidemiological studies, genetic studies, and interventional studies with LDL-C lowering therapies. In addition to LDL-C, other lipid parameters, including total cholesterol, apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), low-density lipoprotein cholesterol (VLDL-C), triglycerides, lipoprotein (a) (Lp [a]), total cholesterol / HDL-C, Apo B/apolipoprotein A1 (ApoA1), HDL-C, and ApoA1, reflect the important aspects of fat metabolism. These parameters correlate to varying degrees with cardiovascular risk.
Currently, preventive measures are considered the most sustainable solution to reduce cardiovascular risk. Interventions leading to LDL-C control in patients with elevated LDL-C and in patients with high cardiovascular risk have reduced the risk of cardiovascular events in these patient populations. Available therapies, such as statins and other lipid-lowering therapies, are effective but in some cases not sufficient or tolerable to reduce LDL-C sufficiently. Therefore, there is still a high unmet medical need.

Beneficial effects

The plasma pharmacokinetics of inclisiran and the pharmacodynamic effects on plasma PCSK9 and LDL-C have been well characterised in healthy subjects and in the intended patient populations.

The primary efficacy endpoints – percentage change in LDL-C from baseline to day 510 and the average percentage change in LDL-C from baseline after day 90 and up to day 540 – were met in all 3 Phase III studies with an 18-month study duration of inclisiran versus placebo:
- in 482 high-risk adult patients with heterozygous familial hypercholesterolaemia (HeFH), as an adjunct to diet, in combination with a statin or a statin with other lipid-lowering therapies in patients who require additional low-density lipoprotein (LDL-C) lowering, the placebo-adjusted percentage reduction of LDL-C from baseline to day 510 was 49.9% ($p<0.0001$), and between day 90 and day 540 was 44.3% ($p<0.0001$) [study ORION-9];
- in 1561 high-risk patients with atherosclerotic cardiovascular disease (ASCVD) and elevated low-density lipoprotein cholesterol (LDL-C) despite maximum tolerated dose of LDL-C lowering therapies, the placebo-adjusted percentage reduction of LDL-C was 57.6% ($p<0.0001$) from baseline to day 510, and 53.8% ($p<0.0001$) between day 90 and day 540 [ORION-10];

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- in 1617 high-risk patients with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C) despite maximum tolerated dose of LDL-C lowering therapies, the placebo-adjusted percentage reduction of LDL-C from baseline to day 510 was 53.5% (p<0.0001), and between day 90 and day 540 was 49% (p <0.0001) [ORION-11].

These results were consistent across all subgroups studied, including gender, age, ethnicity, region, diabetes history, LDL-C baseline, BMI, and background treatments.
Additional support for the clinical relevance of the primary efficacy results is provided by the secondary endpoints (absolute change in LDL-C, percentage change in PCSK9, total cholesterol, Apo-B, and non-HDL-C), whose respective reductions reached statistical significance in all Phase III studies (p <0.001) and were all tested using a hierarchical approach.
Overall, the efficacy results of the submitted Phase III clinical trials show that treatment with inclisiran 300 mg SC on day 1, day 90, day 270, and day 450 as an adjunct to diet, in combination with a statin or a statin with other lipid-lowering therapies, is indicated for the treatment of adults with primary hypercholesterolaemia with existing atherosclerotic cardiovascular disease (ASCVD), or ASCVD-risk equivalents, or patients with heterozygous familial hypercholesterolaemia (HeFH), when an additional reduction of LDL-C is required.

Uncertainties about the beneficial effects

The pronounced temporal disconnect between the plasma PK and the PD effects of inclisiran implies a very long retention of inclisiran in hepatocytes. However, it remains unclear in which form inclisiran persists in human hepatocytes and if any risks arise from this finding.

Based on *in vitro* data, inclisiran has no potential for interactions with CYP enzymes and transporters involved in the metabolism and disposition of xenobiotics. However, no clinical interaction studies were conducted.

The proposed indication not only proclaims treatment with inclisiran of hypercholesterolaemia in combination with a maximum tolerated statin dose, but also alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom statins are contraindicated. In the subgroup analyses of the respective confirmatory Phase III studies, forest plots are used to roughly break down the results according to the presence of statin therapy or other LMT (with relatively low case numbers for no statins / no LMT). Detailed efficacy subgroup analyses showed a consistent benefit with inclisiran in all subjects, regardless of whether they were statin intolerant. These analyses are still based on relatively small numbers. Due to the fundamental differences between inclisiran and statins in terms of chemical structure and mode of action, the contraindications for statins are not directly applicable to inclisiran. Thus, the provided data justify the proposed indication of inclisiran for patients who are statin-intolerant or for whom statins are contraindicated.

Based on the available data, the PD response is not influenced by demographic or other covariates to an extent that would necessitate a dose adjustment or limit the application in certain subgroups of patients. No dose adjustments of inclisiran are necessary across the different renal and hepatic impairment groups. However, no data are available for subjects with severe hepatic impairment or subjects with ESRD under dialysis. Therefore, inclisiran should not be administered to such patients.

Unfavourable effects

The analysis of the cumulative safety data demonstrate the safe use of inclisiran. TEAEs at the injection site were the only adverse events more frequently associated with inclisiran injections, and were usually mild and transient in nature. No other safety risks were identified with inclisiran. In particular, there are no signals regarding hepatic safety, and there is no evidence of an immunogenic potential of inclisiran.

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Uncertainties about the unfavourable effects

Confirmatory Phase III data presented to date demonstrate efficacy and safety of the dosage for up to 18 months. Due to the nature of the disease and the intended indication, even longer or even higher cumulative exposure must be assumed. Rare side effects, side effects with a longer latency period, or side effects caused by prolonged or cumulative exposure can only be adequately substantiated by longer-term data. Three studies on long-term safety are currently ongoing (ORION-4, ORION-3 and ORION-8). The applicant provided an update on these studies up to day 510. Exploratory analyses of the effect of inclisiran on MACE (composite of CV death, resuscitated cardiac arrest, non-fatal MI, ischaemic or haemorrhagic stroke) showed that the number of subjects with a MACE event was similar for placebo- and inclisiran-treated subjects across the 3 studies. The number of subjects with a MACE event was the same for placebo-treated subjects (4.2%) and inclisiran-treated subjects (4.1%) in study ORION-9 and was 10.2% in placebo-treated compared to 7.4% in inclisiran-treated subjects in study ORION-10, and 10.3% compared to 7.8%, respectively, in study ORION-11.
Thus, Leqvio has demonstrated its effect on reducing LDL-C in patients with elevated LDL-C levels, which is an approved surrogate marker for CVD risk. However, a favourable impact on cardiovascular outcomes has not yet been confirmed.
Due to the chronicity of the underlying disease and the exploratory analysis so far, the long-term data in these still ongoing studies need to be followed up.

Benefit-risk conclusion

For treatment with inclisiran 300 mg SC on day 1, day 90, day 270, and day 450 as an adjunct to diet in combination with a maximum tolerated statin dose for the treatment of adults with primary hypercholesterolaemia in existing atherosclerotic cardiovascular disease (ASCVD), or ASCVD-risk equivalents or patients with heterozygous familial hypercholesterolaemia (HeFH), if an additional reduction of LDL-C is required, the overall benefit-risk ratio is positive based on the efficacy results and the currently available benign safety profile. Uncertainties regarding longer-term efficacy outcomes as well as safety data of this novel therapy for the treatment of hypercholesterolaemia still need to be addressed.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to 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 reference document, which is valid and relevant 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. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects.

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:

- 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.

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 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 dosing continued 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 and adolescents

The safety and efficacy of Leqvio in children and adolescents aged under 18 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 anticipated to be 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 passes 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 excluded.

Therefore, a decision must be made whether to discontinue breast-feeding or discontinue/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 in patients who participated in clinical studies (see “Preclinical data”).

Effects on ability to drive and use machines

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

Adverse effects

Summary of the safety profile

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 not known (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 or 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.

Immunogenicity

In 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 EIViS (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 instituted.

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 still reduced 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 and a number of publications the 284 mg dose of inclisiran is equated to 300 mg inclisiran sodium salt or described as such.
The efficacy of inclisiran was evaluated in three phase III studies in patients with atherosclerotic cardiovascular disease (ASCVD) (coronary heart disease, cerebrovascular disease or peripheral arterial occlusive disease), ASCVD risk equivalents (type 2 diabetes mellitus, familial

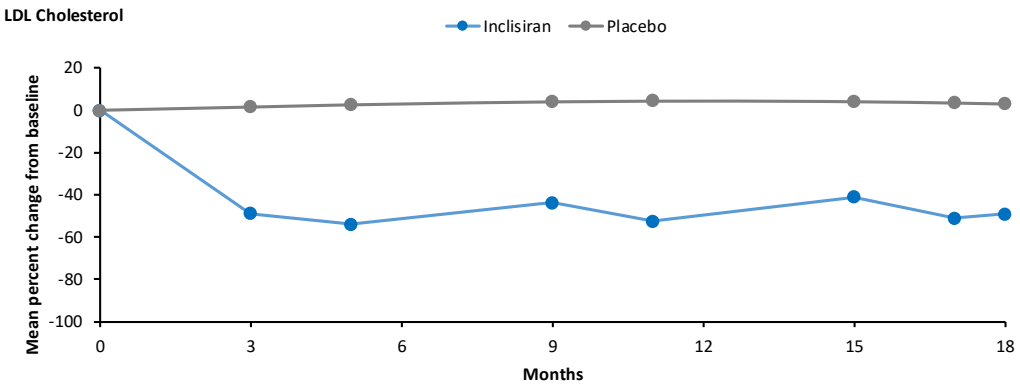
hypercholesterolaemia or 10-year risk of at least 20% of a cardiovascular event assessed by Framingham Risk Score or equivalent) and/or familial hypercholesterolaemia (FH).
Patients were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy and required additional 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 followed 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).

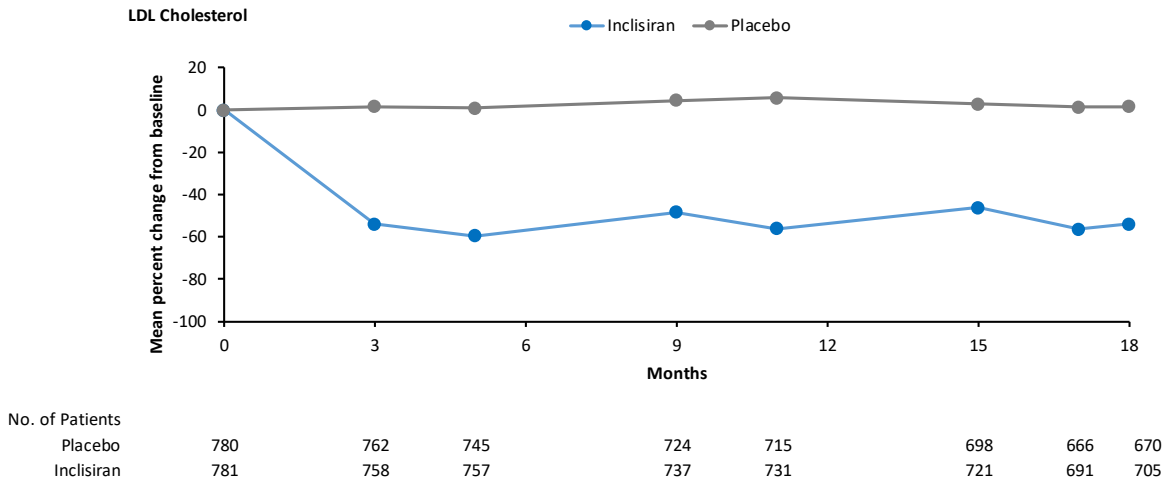
Leqvio also significantly reduced the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 by 54% compared to placebo (95% CI: -56%, -51%; p<0.0001). For additional results see Table 1.

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 study in 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), 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).

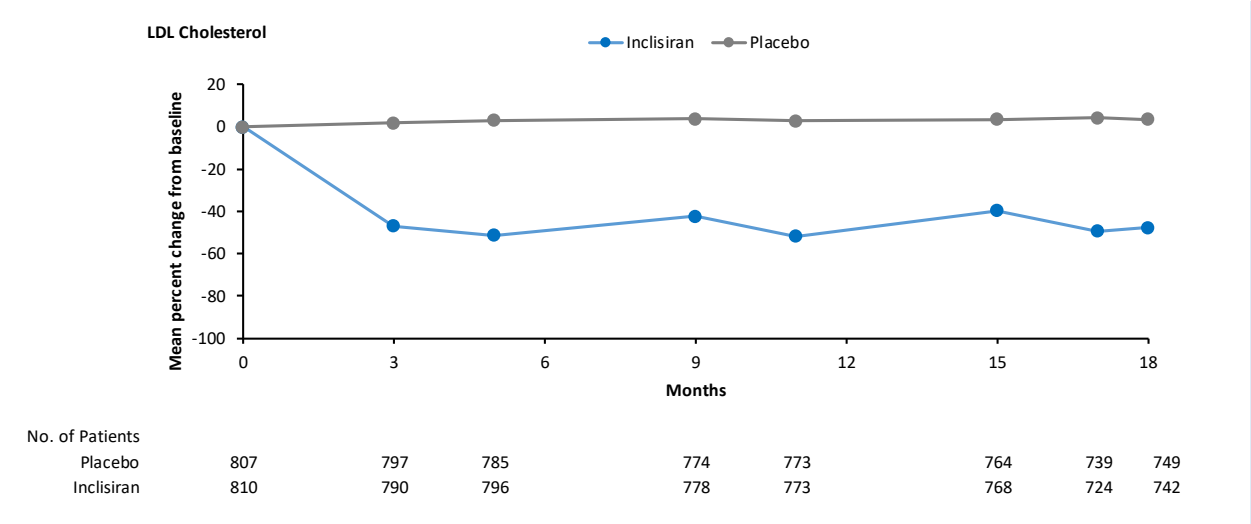
Leqvio also significantly reduced the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 by 49% compared to placebo (95% CI: -52%, -47%; p<0.0001). For additional results see Table 2.

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
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-week 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.

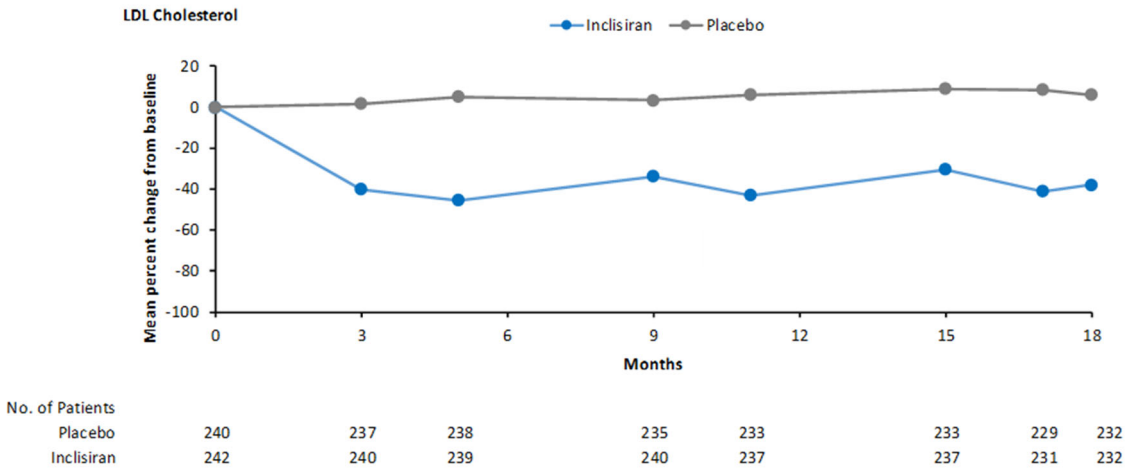
Table 3: Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in the ORION-9 study

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.

Safety and efficacy in paediatric patients

The safety and efficacy of Leqvio in children and adolescents aged under 18 years have not been established. No data are available (see “Dosage/Administration” for information on use in children and adolescents).

Pharmacokinetics

Absorption

Following 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-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 anticipated to be 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 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

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 groups of renal function.
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 (NOAEL) 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 fetal 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

Pack sizes

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

Marketing authorisation holder

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

Information last revised

June 2021