15 October 2020
EMA/696912/2020
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Leqvio

International non-proprietary name: inclisiran

Procedure No. EMEA/H/C/005333/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# Administrative information

| | |
|---|---|
| Name of the medicinal product: | Leqvio |
| applicant: | Novartis Europharm Limited<br>Vista Building<br>Elm Park<br>Merrion Road<br>Dublin 4<br>IRELAND |
| Active substance: | INCLISIRAN |
| International Non-proprietary Name/Common Name: | inclisiran |
| Pharmaco-therapeutic group (ATC Code): | lipid modifying agents, plain, other lipid modifying agents<br>(C10AX) |
| Therapeutic indication(s): | treatment for primary hypercholesterolaemia or mixed dyslipidaemia |
| Pharmaceutical form(s): | Solution for injection |
| Strength(s): | 284 mg |
| Route(s) of administration: | Subcutaneous use |
| Packaging: | pre-filled syringe (glass) |
| Package size(s): | 1 pre-filled syringe |

# Table of contents

**1. Background information on the procedure ..... 12**
1.1. Submission of the dossier ..... 12
1.2. Steps taken for the assessment of the product ..... 13

**2. Scientific discussion ..... 14**
2.1. Problem statement ..... 14
2.1.1. Disease or condition ..... 14
2.1.2. Epidemiology ..... 14
2.1.3. Aetiology and pathogenesis ..... 15
2.1.4. Clinical presentation ..... 15
2.1.5. Management ..... 16
2.2. Quality aspects ..... 17
2.2.1. Introduction ..... 17
2.2.2. Active Substance ..... 18
General information ..... 18
Manufacture, characterisation and process controls ..... 20
Specification ..... 23
Stability ..... 23
2.2.3. Finished Medicinal Product ..... 24
Description of the product and Pharmaceutical development ..... 24
Manufacture of the product and process controls ..... 25
Product specification ..... 25
Stability of the product ..... 26
Adventitious agents ..... 27
2.2.4. Discussion on chemical, pharmaceutical and biological aspects ..... 27
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects ..... 27
2.2.6. Recommendations for future quality development ..... 27
2.3. Non-clinical aspects ..... 28
2.3.1. Introduction ..... 28
2.3.2. Pharmacology ..... 30
2.3.3. Pharmacokinetics ..... 33
2.3.4. Toxicology ..... 36
2.3.5. Ecotoxicity/environmental risk assessment ..... 42
2.3.6. Discussion on non-clinical aspects ..... 42
2.3.7. Conclusion on the non-clinical aspects ..... 43
2.4. Clinical aspects ..... 43
2.4.1. Introduction ..... 43
2.4.2. Pharmacokinetics ..... 47
2.4.3. Pharmacodynamics ..... 51
2.4.4. Discussion on clinical pharmacology ..... 66
2.4.5. Conclusions on clinical pharmacology ..... 67
2.5. Clinical efficacy ..... 68
2.5.1. Dose response studies ..... 68
2.5.2. Main studies ..... 68

2.5.3. Discussion on clinical efficacy ..... 108
2.5.4. Conclusions on the clinical efficacy ..... 112
2.6. Clinical safety ..... 112
2.6.1. Discussion on clinical safety ..... 127
2.6.2. Conclusions on the clinical safety ..... 129
2.7. Risk Management Plan ..... 130
2.8. Pharmacovigilance ..... 133
2.9. New Active Substance ..... 133
2.10. Product information ..... 133
2.10.1. User consultation ..... 133
2.10.2. Additional monitoring ..... 133
**3. Benefit-Risk Balance ..... 134**
3.1. Therapeutic Context ..... 134
3.1.1. Disease or condition ..... 134
3.1.2. Available therapies and unmet medical need ..... 134
3.1.3. Main clinical studies ..... 135
3.2. Favourable effects ..... 136
3.3. Uncertainties and limitations about favourable effects ..... 136
3.4. Unfavourable effects ..... 137
3.5. Uncertainties and limitations about unfavourable effects ..... 137
3.6. Effects Table ..... 138
3.7. Benefit-risk assessment and discussion ..... 140
3.7.1. Importance of favourable and unfavourable effects ..... 140
3.7.1. Balance of benefits and risks ..... 141
3.8. Conclusions ..... 142
**4. Recommendations ..... 142**

# List of abbreviations

| | |
|---|---|
| ACC | American College of Cardiology |
| ADA | Anti-drug antibodies |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| Ago2 | Argonaute RISC Catalytic Component 2 |
| AHA | American Heart Association |
| ALN-PCSSC | Inclisiran |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| Apo-A1 | Apolipoprotein A1 |
| ANOVA | Analysis of variance |
| Apo-B | Apolipoprotein B |
| AS | Antisense |
| ASCVD | Atherosclerotic cardiovascular disease |
| ASGPR | Asialoglycoprotein receptor |
| AST | Aspartate aminotransferase |
| AUC | Area under curve |
| $AUC_{0\text{-}inf}$ | Area under the concentration-time curve from time zero to infinity |
| $AUC_{0\text{-}24h}$ | Area under the curve from time 0 to 24 hours |
| AX-HPLC | anion exchange HPLC |
| BL | Baseline |
| BMI | Body mass index |
| BP | Blood Pressure |
| BUN | Blood urea nitrogen |
| bw | Body weight |
| CHD | Coronary Heart Disease |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |

| | |
|---|---|
| CIOMS | Council for International Organizations of Medical Sciences |
| CL/F | Apparent total clearance from plasma |
| CLR | Renal clearance |
| $C_{max}$ | Maximum observed concentration |
| CMQ | Custom MedDRA query |
| Cosc | Concentration |
| CP | Child-Pugh |
| CPG | Controlled pore glass |
| CPK | Creatine phosphokinase |
| CPP | Critical process parameter |
| CQA | Critical Quality Attribute |
| CrCl | Creatinine clearance |
| CRF | Case report form |
| CRP | C-reactive protein |
| CS | Clinically significant |
| CSR | Clinical study report |
| CV | Cardiovascular |
| CVA | Cerebrovascular accident |
| CVD | Cardiovascular disease |
| CV% | Coefficient of variation % |
| CYP | Cytochrome |
| DBL | Database Lock |
| DBP | Diastolic blood pressure |
| DDI | Drug-drug interaction |
| dL | Decilitre |
| DOE | Design of experiments |
| EAS | European Atherosclerosis Society |
| EC | European Commission |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EEA | European Economic Area |
| eGFR | Estimated glomerular filtration rate |
| ELISA | Enzyme-linked immunosorbent assay |

| | |
|---|---|
| EMA | European Medicines Agency |
| EMSA | Electrophoretic mobility shift assay |
| EOS | End of study |
| ESC | European Society of Cardiology |
| ESRD | End-stage renal disease |
| EtO | Ethylene oxide |
| EU | Endotoxin units |
| EU | European Union |
| FAS | Full analysis set |
| FBS | Foetal bovine serum |
| FDA | Food and Drug Administration |
| FIH | First in Human |
| FH | Familial hypercholesterolaemia |
| Fe | Fraction |
| FPFV | First Patient First Visit |
| FTIR | Fourrier Transform Infrared Spectroscopy |
| GalNAc | N-Acetylgalactosamine |
| GAPDH | Glyceraldehyde 3-phosphate dehydrogenase |
| GCP | Good clinical practices |
| GFR | Glomerular filtration rate |
| GLP | Good laboratory practices |
| GMP | Good manufacturing practices |
| HBA1c | Glycated haemoglobin A1c |
| HDL-C | High density lipoprotein cholesterol |
| HPDE | High Density Polyethylene |
| HeFH | Heterozygous familial hypercholesterolaemia |
| HF | Hepatic function |
| HI | Hepatic impairment |
| HLM | Human liver microsomes |
| HoFH | Homozygous familial hypercholesterolaemia |
| hPCSK9 | Human proprotein convertase subtilisin/kexin type 9 |
| HPLC | High performance liquid chromatography |
| HR | Heart rate |

| | |
|---|---|
| hsCRP | High sensitivity C-reactive protein |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| $IC_{50}$ | Plasma concentration yielding 50% of maximal inhibition |
| INR | International normalised ratio |
| IPRP-HPLC | Ion-pair reversed phase HPLC |
| IR | Infrared |
| IRB | Institutional review board |
| ISAP | Integrated Statistical Analysis Plan |
| ISS | Integrated Summary of Safety |
| ITT | Intent-to-treat |
| ITT | Intention to Treat |
| kg | Kilogram |
| LC-MS | Liquid chromatography mass spectrometry |
| LDL | Low-density lipoprotein |
| LDL-C | Low-density lipoprotein cholesterol |
| LDLR | Low Density Lipoprotein Receptor |
| LLN | Lower limit of normal |
| LLOQ | Lower limit of quantitation |
| LMT | Lipid-modifying therapy |
| Lp(a) | Lipoprotein (a) |
| Lp-PLA2 | Lipoprotein-associated phospholipase A2 |
| LOESS | locally weighted scatterplot smoothing |
| LS | Least Squares |
| MAA | Marketing authorisation application |
| mAbs | Monoclonal Antibodies |
| MACE | Major cardiovascular event |
| MAD | Multiple ascending dose |
| MAR | Missing-at-random |
| MD | Multiple-dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |

| | |
|---|---|
| mL | Milliliter |
| MI | Myocardial Infarction |
| mITT | Modified intent-to-treat |
| mmHg | Millilitres of mercury |
| mmol | Millimole |
| MMRM | Mixed Model for Repeated Measures |
| mRNA | Messenger ribonucleic acid |
| MS | Mass Spectrometry |
| MTD | Maximum tolerated dose |
| MTP inhibitor | Microsomal Triglyceride Transfer Protein Inhibitor |
| MNAR | Missing Not at Random |
| $m^2$ | Meter squared |
| n | Number of patients |
| N/A | Not applicable |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NAFLD | Non-alcoholic fatty liver disease |
| NASH | Non-alcoholic steatohepatitis |
| NCA | Non-compartmental analysis |
| NLT | Not less than |
| NMR | Nuclear Magnetic Resonance |
| NMT | Not more than |
| No | Number |
| NOD | New onset of diabetes |
| Non-HDL-C | Non High Density Lipoprotein Cholesterol |
| NQ | Not quantifiable |
| ng | Nanogram |
| PBS | Protein binding system |
| PCS | Potentially clinically significant |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| PD | Pharmacodynamic |
| PDCO | Paediatric committee |
| PFS | Pre-filled syringe |

| | |
|---|---|
| Ph. Eur. | European Pharmacopoeia |
| PI | Product information |
| PIP | Paediatric investigation plan |
| PK | Pharmacokinetic |
| PMM | Pattern Mixture Model |
| Pos | Positive |
| PP | Polypropylene |
| PPQ | Process performance qualification |
| PT | Preferred term |
| QP | Qualified person |
| QTc | QT interval corrected |
| QTcF | QT interval corrected Fridericia correction |
| QTPP | Quality target product profile |
| QWBA | Quantitative whole body autoradiography / autoradioluminography |
| REC | Recommendation |
| REML | Restricted maximum likelihood |
| RISC | Ribonucleic acid-induced silencing complex |
| RNA | Ribonucleic acid |
| RNAi | Ribonucleic acid interference |
| RRT | Relative retention time |
| S | Sense |
| SAD | Single-ascending dose |
| SAE | Serious adverse event |
| SBP | Systolic blood pressure |
| SC | Subcutaneous |
| SAD | Single ascending dose |
| SD | Standard deviation |
| siRNA | Small interfering ribonucleic acid |
| SmPC | Summary of product characteristics |
| SMQ | Standardised MedDRA query |
| SOC | System organ class |
| Statin | HMG-CoA (3-hydroxy3-methyl-glutaryl-coenzyme A) reductase inhibitor |
| TC | Total cholesterol |

| | |
|---|---|
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| TG | Triglycerides |
| $T_{max}$ | Time to maximum concentration observed |
| TNF-α | Tumour necrosis factor-alpha |
| $t_{½}$ | Elimination half-life |
| UHPLC-TOF-MS | ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry |
| ULN | Upper limit of normal |
| ULOQ | upper limit of quantification |
| US | United States |
| USA | United States of America |
| USP | United States Pharmacopoeia |
| UV | Ultraviolet |
| Vz/F | Volume of distribution |
| WHO | World Health Organisation |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Novartis Europharm Limited submitted on 9 January 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Leqvio, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 March 2019.

The applicant applied for the following indication:

*Hypercholesterolaemia and mixed dyslipidaemia*

*Inclisiran is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial)*

*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.*

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *Information on paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0321/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0321/2018 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## New active substance status

The applicant requested the active substance inclisiran contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

### *Scientific advice*

In 2017, the applicant received scientific advice from CHMP (EMEA/H/SA/3532/1/2017/III) regarding the toxico-pharmacological and clinical development. This was further substantiated by the scientific advice clarification letter from 18 May 2017 in which the dose selection of 300 mg for the phase III programme and the design of the pivotal LDL-C lowering studies was agreed.

In 2018, the applicant received scientific advice from CHMP (EMEA/H/SA/3532/2/2019/I) regarding questions on chemical, pharmaceutical, and biological development.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Ewa Balkowiec Iskra

| | |
|---|---|
| The application was received by the EMA on | 9 January 2020 |
| The procedure started on | 30 January 2020 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 20 April 2020 |
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 20 April 2020 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 4 May 2020 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 28 May 2020 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 16 July 2020 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 17 September 2020 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 21 September 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 30 September 2020 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Leqvio on | 15 October 2020 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Leqvio is proposed to be used in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) 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 low-density lipoprotein cholesterol (LDL-C) goals with the maximum tolerated dose of a HMG-CoA reductase inhibitor (statin) or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Primary hypercholesterolaemia by definition is any hypercholesterolaemia that is caused by a disturbance (familial- or nonfamilial) in the lipid metabolism and is not caused by another condition, such as hypothyroidism, or a drug effect. The heterozygous familial form of this condition [heterozygous familial hypercholesterolaemia (HeFH)] is rare and is estimated to occur in 1:500 individuals globally. LDL-C levels in affected individuals are elevated and in spite of aggressive statin use there is still a 2-fold excess of coronary heart disease (CHD) related deaths relative to age-matched controls within this population.

Hypercholesterolaemia is caused by an increased level of cholesterol in the blood. Primary hyperlipidaemia is usually due to genetic causes (monogenetic or polygenetic) and environmental factors, such as diet and lifestyle and primary nonfamilial hyperlipidaemia is a kind of hyperlipidaemia that is not due to a specific genetic disorder, but due to polygenetic influences. Mixed dyslipidaemia is generally defined as elevated LDL-C and high triglycerides and/or low high-density lipoprotein cholesterol (HDL-C).

A strong positive correlation and causal relationship between LDL-C levels and risk of cardiovascular disease (CVD) has been derived from a large body of clinical and epidemiological studies. There is also a strong relationship to other clinical manifestations in the body like cerebrovascular disease (i.e. ischaemic stroke) or peripheral vascular disease. Epidemiologic data indicate a continuous increasing relative risk of CVD from very low to high levels of LDL-C, with a higher absolute risk in patients at the higher end of LDL-C levels.

### 2.1.2. Epidemiology

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide. There are multiple factors that contribute to the development. The main factor, which is derived from numerous clinical studies, genetic examinations, and epidemiological surveys, is an elevated LDL-C level, which increases the risk to develop atherosclerotic coronary heart disease.

Data from several studies emphasise the importance of targeting cholesterol reduction for both primary and secondary prevention of reducing cardiovascular (CV) events and this is supported by current US and EU recommendations. As these recommendations recognise that the LDL-C goals are not always achievable by maximum tolerated statin therapy alone, an unmet medical need remains and additional LDL-C lowering therapies are necessary[3].

Data from several clinical studies suggest that the greater the LDL-C reduction will be, the greater the declines in ASCVD-associated morbidity and mortality can be expected.

Although several classes of LDL-C-lowering drugs are currently available, there is still a need for new effective and safe treatment options.

### 2.1.3. Aetiology and pathogenesis

Based on epidemiological evidence a strong positive correlation and causal relationship between serum LDL-C and the risk of atherosclerotic vascular damage exists which leads to CHD, CVD, and peripheral vascular disease by developing atheromatous vascular debris that leads to a constriction of the vascular lumen and thus to circulatory disorders.

The European Atherosclerosis Society (EAS) released a consensus statement in the year 2017 to confirm the "LDL-C hypothesis" by stating that "there is a dose-dependent, log-linear association between absolute LDL cholesterol and cardiovascular risk, and this association is independent of other cardiovascular risk factors and is consistent across the multiple lines of evidence".

Statins are today the gold standard for treating elevated LDL-C levels. A 25% proportional reduction in the risk of coronary revascularisation procedures was observed with statin therapy or a more intensive statin regimen per 1 mmol/L lower LDL-C. Statins reduce LDL-C levels by inhibiting HMG-CoA reductase (also known as 3-hydroxy3-methyl-glutaryl-coenzyme A reductase). Recent studies demonstrated that the administration of lipid-lowering agents such as ezetimibe on top of statins further reduce LDL-C levels and the CVD event rate compared to monotherapy.

The reduction rates for lipid-modifying agents are at about 50% for high-intensive statin therapy, about 15% to 30% for ezetimibe, about 13% to 20% for bile acid sequestrants, and about 43% to 64% for PCSK9 inhibitors, respectively.

The results of these clinical studies have sufficiently demonstrated the direct association between LDL-C reduction and CV risk reduction across a wide variety of patient populations with different cardiovascular risks.

Results from recent studies with the new PCSK9-inhibitors evolocumab and alirocumab also demonstrated the strong relationship between LDL-C reduction and CV risk reduction and that there is currently no lower limit below which lowering LDL C is not beneficial.

### 2.1.4. Clinical presentation

The underlying atherosclerotic vascular lesions that cause CHD, CVD, and peripheral vascular occlusive disease are vascular lesions caused by an elevated LDL-C level. An outstanding role to reduce the risk of major CV events is lowering of LDL-C, which has been established for a long time. Data to support the relationship between LDL-C and CV events and specifically the relationship with inhibition of PCSK9 has been shown in genetic studies of variations in the genes that influence LDL-C and from studies in patients with familial hypercholesterolaemia (FH). In Mendelian randomisation studies evaluating multiple genetic targets that impact LDL-C levels, the variants in genes that regulate LDL-C levels

(e.g., LDL-R, PCSK9) have demonstrated that lowering of LDL-C is associated with a lower risk for CV events[1] [2].

To minimise this risk factor, lipid-lowering therapies are recommended in the primary and secondary prevention of ASCVD. To reach this goal, specific targets have been suggested. It has been shown that the higher the CV risks, the more aggressive the lipid-lowering therapy should be.

### 2.1.5. Management

Today available lipid-lowering therapies include:

- Statins (oral administration) are the gold standard in LDL-C reduction and have been extensively evaluated in numerous clinical studies in patients with a wide range of CV risk profiles. The 2019 'ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk' focus on the benefits of statin therapy while non-statin therapies like ezetimibe or PCSK9-inhibitors can provide additional benefit or can be used as monotherapies in statin-intolerant patients.
- Ezetimibe (oral administration) is used as add-on therapy when treatment goals have not been achieved with statins or as monotherapy when statins are not tolerated or contraindicated. CV benefits have been demonstrated in patients with established CVD.
- Fibrates (oral administration) and bile acid sequestrants (oral administration) are less efficacious than statins at LDL C lowering and have a less favourable side effect profile compared to statins. Cardiovascular benefits of these lipid-modifying agents have not been demonstrated satisfactorily.
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (SC administration) can be used as add-on therapy to maximum statin treatment when treatment goals have not been achieved with statins or when statins are not tolerated or contraindicated. CV benefits have already been demonstrated in patients with established CVD.

## *About the product*

Mode of action

Inclisiran (ALN-PCSSC) is a chemically modified double-stranded 21-23mer small interfering RNA (siRNA), conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. It is an injectable LDL-C lowering drug being developed for the treatment of patients with hyperlipidaemia.

Inclisiran inhibits the translation of PCSK9 in the liver cell thus preventing the degradation of the LDL-receptor (LDLR) on the cell surface, which leads to a reduction of LDL-C.

[1] Kathiresan S. et al. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet. 2009 Jan;41(1):56-65.
[2] Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, Voros S, Giugliano RP, Davey Smith G, Fazio S, Sabatine MS. Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes. N Engl J Med. 2016 Dec 1;375(22):2144-2153.

Proposed Indication

Inclisiran is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) 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.

Recommended dose

The recommended dosage of inclisiran is 284 mg administered as a single subcutaneous (SC) injection: initially, again at 3 months and then every 6 months.

## *Type of Application and aspects on development*

***Accelerated assessment***

Not requested by the applicant.

***Conditional marketing authorisation***

Not requested by the applicant and not proposed by the Rapporteur.

***Marketing authorisation under exceptional circumstances***

Not requested by the applicant and not proposed by the Rapporteur.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as solution for injection in pre-filled syringe containing 284 mg of inclisiran. The product contains the inclisiran sodium salt (300 mg inclisiran sodium in 1.5 ml aqueous solution equivalent to 284 mg of inclisiran). It is intended to be administered as a subcutaneous injection

Other ingredients are water for injections, sodium hydroxide (for pH adjustment), concentrated phosphoric acid (for pH adjustment).

The product is available in 1.5 ml solution in a pre-filled syringe (Type I glass) with plunger stopper (bromobutyl, fluorotec coated rubber) with needle and rigid needle shield, as described in section 6.5 of the SmPC.

## 2.2.2. Active Substance

***General information***

Inclisiran sodium is a synthetic, chemically modified, double-stranded, small interfering ribonucleic acid (siRNA). The sense strand contains 21 nucleotides and the antisense strand contains 23 nucleotides. The sense strand is conjugated with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes.

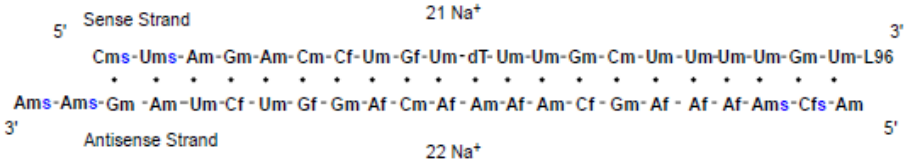
The molecular formula of inclisiran sodium is $C_{529}H_{664}F_{12}N_{176}Na_{43}O_{316}P_{43}S_6$ (salt form) and molecular weight is 17,284.75 g/mol (salt form). The molecular formula and molecular weight of inclisiran sodium are summarised in Table 1.

**Table 1: active substance molecular formula and molecular mass**

| | Inclisiran | Sense strand | Antisense strand |
|---|---|---|---|
| Molecular formula of the sodium salt | $C_{529}H_{664}F_{12}N_{176}Na_{43}O_{316}P_{43}S_6$ | $C_{292}H_{395}F_2N_{75}Na_{21}O_{182}P_{21}S_2$ | $C_{237}H_{269}F_{10}N_{101}Na_{22}O_{134}P_{22}S_4$ |
| Molecular formula of the free acid | $C_{529}H_{707}F_{12}N_{176}O_{316}P_{43}S_6$ | $C_{292}H_{416}F_2N_{75}O_{182}P_{21}S_2$ | $C_{237}H_{291}F_{10}N_{101}O_{134}P_{22}S_4$ |
| Molecular weight of the sodium salt (g/mol) | 17,284.72 | 9,103.01 | 8,181.71 |
| Molecular weight of the free acid (g/mol) | 16,339.51 | 8,641.40 | 7,698.11 |

The active substance structure is illustrated in Figure 1and Figure 2. In Figure 1, the bases involved in a base pair formation are connected with a centre dot. The structure of L96, the N-acetylgalactosamine (GalNAc) containing moiety, is also provided. In Figure 2, the structure is represented using an expanded structural formula showing the phosphate backbone. The bases involved in a base pair formation in this case are connected with a dotted line.

**Figure 1: active substance structure**




**Inclisiran Sodium**

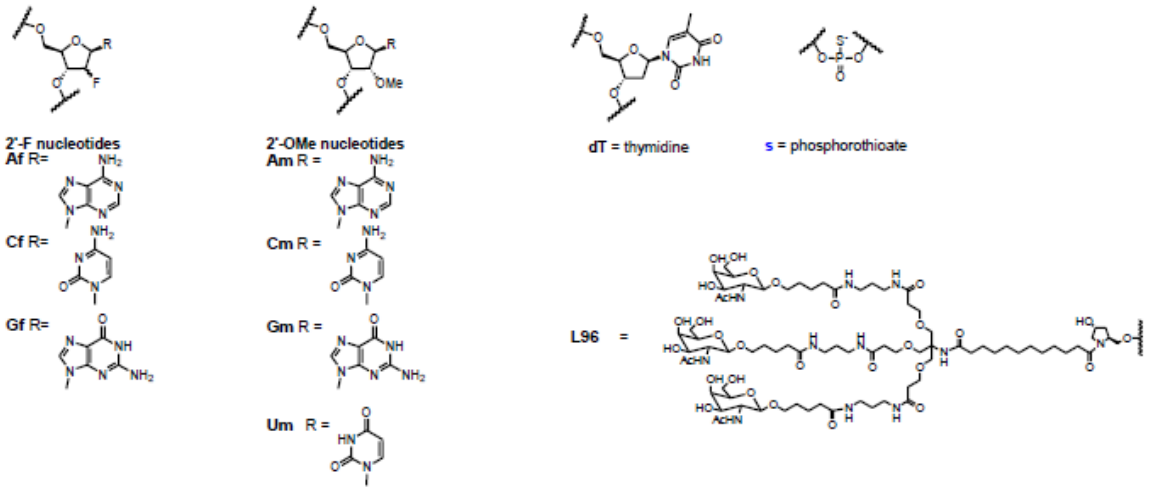
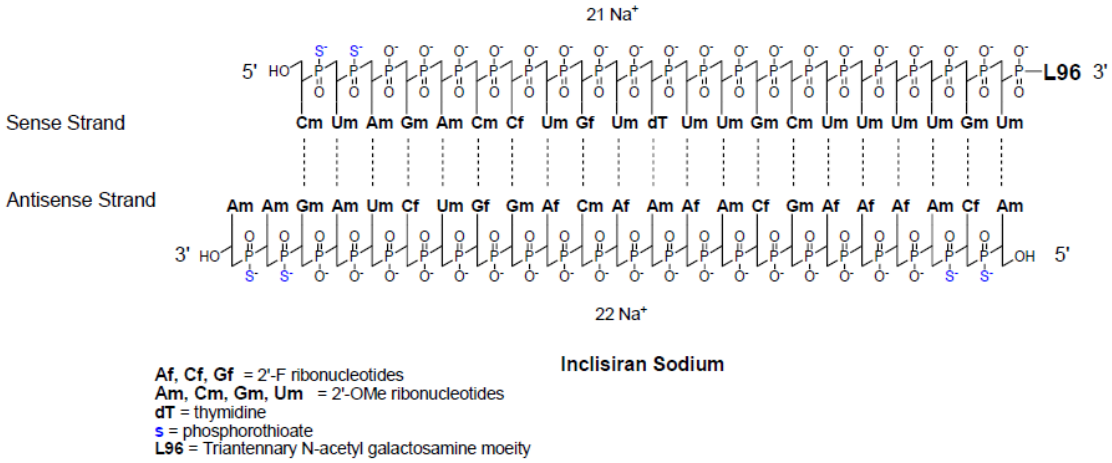


**Figure 2 : expanded active substance structure**




**Inclisiran Sodium**

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

The active substance is a white to pale yellow hygroscopic powder. In order to mitigate the potential adverse effects of hygroscopicity, the active substance is packaged in wide mouth high density polyethylene (HDPE) bottles with polypropylene screw closures. The HDPE bottles are placed into foil bags, which serve as a secondary moisture barrier. Stability of the active substance has been established in the same container closure system demonstrating good control of moisture content.

The solubility of inclisiran sodium in water is at least 300 mg/ml at ambient conditions. Solubility of inclisiran sodium in acetonitrile, methanol, isopropyl alcohol and other organic solvents is negligible due to the highly polar nature of the oligonucleotide active substance. The results are consistent with the very poor lipophilicity expected from a highly charged oligonucleotide.

The chemical structure of inclisiran sodium was elucidated and characterised by a combination of orthogonal analytical techniques.
The structure elucidation data are considered acceptable to confirm the correct sequences of the single strand intermediates and the duplex structure of the inclisiran active substance.

The stereochemistry of inclisiran sodium is complex and is controlled in the synthesis of the single strands. There are chiral centre contributions from three components of the active substance summarised below.

*1. The nucleotides;* Each adenosine (A), guanosine (G), uridine (U) and cytidine (C) nucleotide introduces four chiral centres and each thymidine (dT) introduces three chiral centres into the single strands. The chiral centres associated with the phosphoramidites are not labile and inversion of stereochemistry at these centres is not expected to occur under the conditions of detritylation, coupling, capping, deprotection or cleavage associated with the synthesis of the single strands, or the subsequent steps leading to the active substance.

*2. The GalNAc (L96) moiety;* Two components in the GalNAc structure, galactosamine and trans-4-hydroxy-L-proline methyl ester contribute to the chiral centres of GalNAc. The galactosamine and trans-4-hydroxy-L-proline methyl ester are both of natural origin and their stereochemistry is established by the biological source.

*3. Phosphorothioate groups;* The phosphorothioate groups (4 in the antisense strand and 2 in the sense strand) are formed by a reaction that is not stereospecific. The stereochemical outcome is expected to be consistent from batch to batch. The control strategy for ensuring the consistent stereochemistry of inclisiran sodium final active substance is considered acceptable. A test method was developed that can reliably separate the diastereoisomers. The distribution of the peaks is consistent across batches within each single strand, and comparable to batches used in toxicology studies.

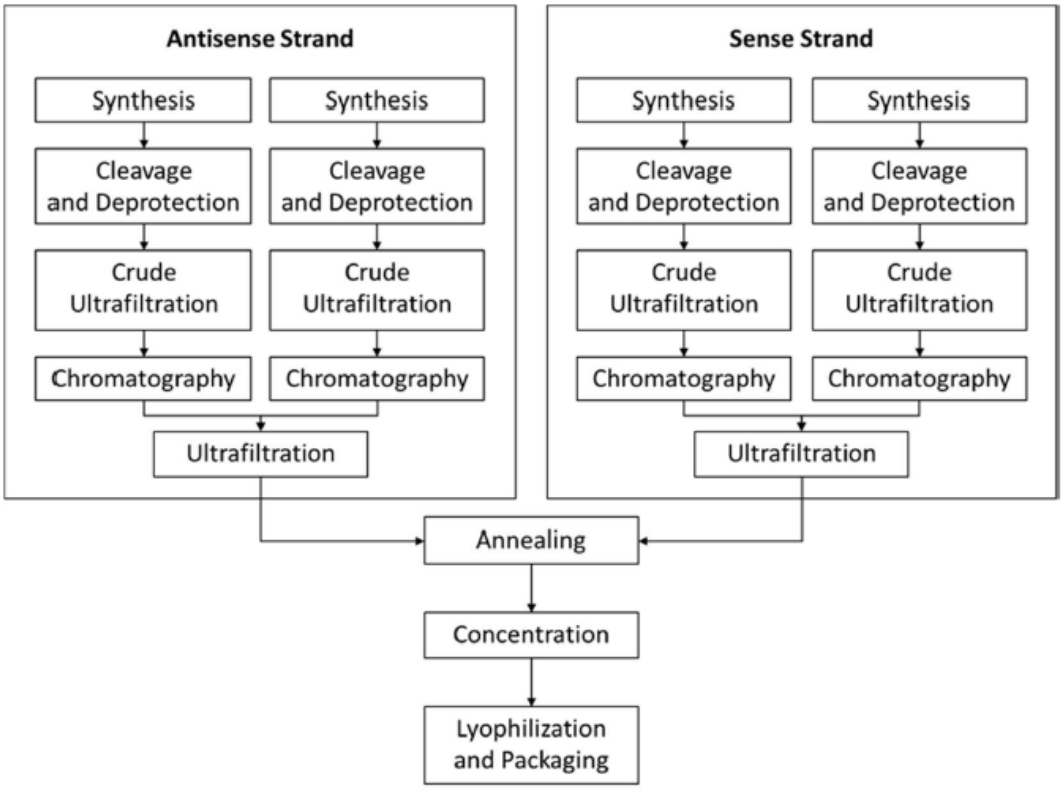
***Manufacture, characterisation and process controls***

Inclisiran sodium is manufactured in seven main steps using well defined starting materials with acceptable specification as summarised in Figure 3. The manufacturing process consists of synthesizing the two single strand oligonucleotides (sense and antisense strands) by conventional solid phase synthesis using 3'-O-(2-cyanoethyl) phosphoramidite chemistry with the 5'-hydroxyls protected with 4,4'-dimethoxytriphenylmethyl (DMT) groups and fluoro-, OMe- or deoxy-modifications at the 2'-position.

The sense strand is synthesised on protected GalNAc-containing-ligand (i.e., L96) loaded polymer support. The antisense strand is synthesised on 2'-OMe A-loaded controlled pore glass (CPG) support.

The synthesised single strand oligonucleotides are cleaved from the solid support, deprotected, and after an ultrafiltration step, purified by HPLC. Purification is followed by a second ultrafiltration step, to remove the components of the mobile phases used in the chromatography. The two single strands are mixed in a targeted equimolar ratio during annealing, followed by concentration and lyophilisation.

**Figure 3: active substance manufacturing process - main steps**




The manufacturing scale is defined based on the loading of the synthesis solid support.

Additional ultra/diafiltration and lyophilisation steps are stated as potential reprocessing steps. No reprocessing has been performed yet and the applicant commits to perform investigations and inform the authorities if reprocessing is required.

The starting materials used in the preparation of inclisiran sodium include eight phosphoramidites, 2'-OMe A Controlled Pore Glass (CPG) and fully acetylated triantennary N-acetylgalactosamine trans-4-hydroxyprolinol-O-DMT succinate (protected GalNAc [L96]) polymer support - Protected GalNAc-PS).

Protected phosphoramidites are considered suitable starting materials for synthetic oligonucleotides. An appropriate justification for the classification of phosphoramidites as starting materials has been provided. Detailed information on the impurity profiles of the phosphoramidite starting materials and their classification into critical and non-critical impurities has been provided. Critical impurities can be incorporated into the active substance during various steps of synthesis cycle. Impurity species that cannot be incorporated into the oligonucleotide during synthesis and thus do not impact the purity of the final product are considered non-critical. The phosphoramidite specifications have been set taking into account the limited available batch data and the applicant has committed to re-evaluate and tighten the specification limits of the phosphoramidite starting materials when data from a sufficient number of commercial active substance batches (additional 18 batches) will be available (REC1).

A detailed description of the synthesis of the GalNAc-PS starting material has been provided, together with results of batch analysis of several batches, characterisation of the impurity profile, control of the GalNAc-PS and also its precursor in the synthesis and discussion of fate and purge of impurities present in GalNAc-PS. These data are considered appropriate to substantiate controlled and consisted quality of the proposed starting material GalNAc-PS considering that this starting material is complex. Analytical validation data for the methods applied in the specification have been provided.

Controlled pore glass (CPG) loaded with nucleotides are a class of long standing and commercially available supports for oligonucleotide synthesis. 2'-OMe A CPG is manufactured by the chemical modification of native CPG beads to generate beads bearing a long chain amine group. The amine group is coupled with 2'-OMe A succinate to attach the nucleotide to the support.

The selection of all starting materials has been carried out according to the principles of ICH Q11, i.e. they all have defined physical and chemical properties and structure; they are incorporated as a structural fragment into the structure of the inclisiran; they are purchased from commercial suppliers; and they are controlled with specifications to ensure inclisiran active substance quality. The selection of the starting materials is considered adequately justified taking into account also the manufacturing process which includes numerous cycles of various steps, including purification steps, which altogether ensure the proper purge of starting materials' potential related and degradation impurities preventing their carry over to single strand intermediates or even final inclisiran active substance. Critical and non-critical impurities from starting materials have been identified and the proposed acceptance limits provided. This classification is mostly related to the potential reactivity or non-reactivity of these impurities, respectively, and the consequent impact on the quality of the intermediate single strand oligonucleotides and the final inclisiran DS. Suppliers of the starting materials are listed in the dossier. Confirmation that the addition of an alternative vendor for the starting materials will applied for by variation has been provided.

A list of all reagents, solvents, and auxiliary materials used in the active substance manufacturing process is provided. Adequate specifications have been provided for each of the raw materials.

The principles of criticality assessment and risk analysis are adequately addressed. Critical quality attributes (CQA), critical process parameters (CPP) and process parameters (PP) have been defined. The critical process steps and associated CPPs for each unit operation and the non-critical process parameters of the manufacturing process are summarised. Proven acceptable ranges have been defined for the CPPs. These proven acceptable ranges are acceptable and have been justified in the process refinement studies.

The quality of double-stranded oligonucleotides is pre-determined by the quality of the single strand precursors. Therefore, the control of these intermediates by adequate specifications is essential. Identity by molecular weight and retention time but more importantly by sequencing is performed for the sense and antisense strand. Consequently, the sequence is proven also for the resulting duplex.

Purity of the sense and the antisense strand is determined by two techniques, AX-HPLC and IPRP-HPLC.

The specified impurities for the sense strand are grouped based on their retention times and controlled within defined limits for each group. This is acceptable as it is commonly applied for synthetic oligonucleotide products. Batch analysis for 12 batches of sense and antisense strand have been provided, respectively. The proposed limits for purity of specified impurities, total unspecified and total impurities in the single strands are acceptable. The applicant has committed to re-evaluate the specification limits for the single strand intermediates when data from a sufficient number of commercial active substance batches (additional 18 batches) will be available (REC2).

A three-stage lifecycle approach is applied for process validation of the active substance manufacturing process. This approach is acceptable and a statement has been provided that active substance process validation will be finalised prior to marketing of the resulting finished product. The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. Information on batch history from development through validation has been provided. The main changes during development were change 1 (a scaled-up process) and change 2 (a finalised refined process to be used for the validation). All changes are described in detail and the influence on active substance quality has been sufficiently investigated and described. The characterisation reports for process refinement (change 2) were provided. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

As per ICH Q3A, impurities are classified into organic impurities, inorganic impurities and residual solvents. The organic impurities are further classified into process-related impurities and product-related impurities.

Product-related oligonucleotide impurities are formed during the manufacturing process or during storage, including degradants. These impurities are controlled by the manufacturing process and long term storage conditions by two orthogonal HPLC techniques (AX-HPLC and IPRP-HPLC) in the single strand intermediates and the final active substance.

impurities are deletion (shortmers) and addition (longmers) impurities, partially deprotected oligonucleotide chains that are not fully deprotected or improperly deprotected during manufacture, phosphodiester (P=O) impurities, where a phosphodiester replaces the thiophosphate (P=S) in the sense and antisense strands, impurities carried over from parent starting material impurities and in particular those associated with the triantennary N-acetyl galactosamine (GalNAc) portion of the sense strand.

In general, a good understanding of the impurity profile in the single strand intermediates and the final active substance has been demonstrated. Impurity monitoring is performed on impurities grouped by adjusted RRT ranges which is acceptable for synthetic oligonucleotides with an extremely complex impurity profile. Process related organic impurities have been discussed and are considered removed due to extensive washing, chromatographic and ultrafiltration steps.

The evaluation of the presence of genotoxic materials in the active substance is performed in accordance with the principles stipulated in the ICH M7 guideline. It is agreed that based on the very large purge factors associated with the steps downstream of synthesis, there is no risk associated with

these potential impurities to the quality of the final active substance and therefore no need to be monitored.

There are no class 1 solvents used in the manufacturing of inclisiran active substance. A number of class 2 and class 3 solvents are used in the manufacturing process. Sufficient data have been provided to justify that only acetonitrile will be controlled in the active substance specification. Inorganic impurities have been sufficiently addressed. The packaging materials comply with the Regulations EC 10/2011 as amended.

***Specification***

The active substance specification includes tests for appearance, identity by duplex retention time (IPRP-HPLC-UV), identity by single strand MW (IPRP-HPLC-UV ESI MS, non-denaturing), identity by Tm (UV spectrophotometry), identity of single strands by sequence (MS-MS fragmentation), sodium content (Ph. Eur.), purity non-denaturing (IPRP-HPLC-UV), purity denaturing (AX-HPLC UV), purity denaturing (IPRP-HPLC-UV), assay (UV absorption), pH (Ph. Eur.), water content (Ph. Eur.), acetonitrile (headspace GC FID), bacterial endotoxins (Ph. Eur.), and bioburden (Ph. Eur.).

The active substance specification attributes are acceptable The concept of grouping of impurities as proposed in the specification is acceptable. The proposed control of impurities is acceptable.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. Sufficient information on reference standards and materials and the container closure system has been provided.

The identity of the single strands is determined by sequencing of the single strands intermediates during the synthesis, as per the intermediate specifications. Batch analysis data from twelve batches of the active substance were provided. The results are within the specifications and consistent from batch to batch. The applicant has committed to re-evaluate the active substance specification limits when data from a sufficient number of commercial active substance batches (additional 18 batches) will be available (REC3).

***Stability***

Stability data from 11 batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 60 months* under long term freezer conditions (-20°C ± 5°C) and for up to 6 months under accelerated conditions (25°C ± 2°C / 60 ± 5% RH) according to the ICH guidelines were provided.

(*Data for up to 60 months (1 batch), 36 months (1 batch), 30 months (3 batches), 18 months (1 batch), 12 months (1 batch), 6 months (3 batches) and 3 months (1 batch) were provided.)

The quality attributes tested under the storage conditions are appearance, assay, water content, purity by non-denaturing IPRP-HPLC, purity by denaturing AX-HPLC, purity by denaturing IPRP-HPLC, bioburden and bacterial endotoxins. No changes or trends have been observed at long term or accelerated conditions with the exception of noticeable degradation at accelerated conditions for purity by denaturing IPRP-HPLC.

Forced degradation studies have been performed. The stress conditions studied are temperature, acid, base, oxidation and light (in line with ICH Q1B). Acceptable mass balance was demonstrated supporting the use of the three purity methods as stability indicating. Significant degradation was observed at high temperatures and under acid, base and oxidation conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months stored in freezer conditions (-20 ± 5 °C) in the proposed container.

## 2.2.3. Finished Medicinal Product

***Description of the product and Pharmaceutical development***

The finished product is a sterile solution in a prefilled syringe (PFS). Each PFS unit contains 284 mg inclisiran (equivalent to 300 mg inclisiran sodium) in 1.5 mL water for injection.

The container closure for PFS is a 2.25 mL Type I clear glass syringe with a staked needle and rigid needle shield and a bromobutyl fluorotec coated plunger. The final assembly of the syringe also include a standard plunger rod and a finger flange installed during secondary packaging.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The pharmaceutical development is adequately described in the dossier. The quality target product profile (QTPP) was defined. A list of critical process parameters (CPP) and the corresponding critical quality attributes (CQAs) were identified.

The finished product contains the active substance dissolved in WFI with sodium hydroxide or phosphoric acid added for pH adjustment. For an adequate subcutaneous application, a target pH of 7 was defined. The composition of the finished product used throughout all clinical development was the same as proposed for commercial formulation.

The manufacturing process consists of bulk solution preparation and sterile filtration plus aseptic filling. Compatibility of the bulk solution with the manufacturing equipment was tested. The equipment was found to have no negative impact on the finished product quality based on the impurity profiles of three finished product batches compared to the profiles of the three active substance batches used for the manufacture of the finished product batches. Bulk hold time was also evaluated. Hold time studies for the bulk solution were part of the process validation. The selection of sterile filtration and aseptic filling as the sterilisation process has been sufficiently justified in accordance with EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015) and Ph. Eur. chapter 5.1.1. Given the thermally sensitive nature of the active substance, terminal sterilization using either moist or dry heat or even post aseptic treatment heating options are not useable options and lead to greater risk to product quality than the use of sterile filtration. The use of ionizing radiation has been demonstrated to lead to extensive degradation on nucleic acid formulations, especially at the proposed 25 Gy exposure level. The generation of new additional impurities and extensive degradation are risks to product quality not associated with sterile filtration. Gas sterilization uses alkylating or oxidizing agents known to be highly reactive towards nucleic acids, therefore it is not useable for a formulation such as inclisiran.

Validation of the sterilizing filter covered a bacterial challenge study. Filter validation is supplemented with sufficient data and discussion on potential sorption of solution components to the filters and extractable and leachables from the filters.

An overfill of 0.03 mL of the pre-filled syringes to allow for 1.5 mL delivered volume have been defined. The overfill has been derived from a fill volume study. The primary packaging is a 2.25 mL Type I glass siliconised syringe with a staked needle and a rigid needle shield and a bromobutyl flurotec coated

plunger. The materials comply with Ph. Eur. and EC requirements. The glass syringe is supplied sterilised (EtO sterilisation), the plunger ready to sterilise. The compatibility of the glass syringe and the plunger with the finished product has been demonstrated based on the stability studies and on extractable/leachables studies. At time zero and 6 months (25 °C and 40 °C) no leachables of concern were found. The stability study will continue until 36 months of storage of the primary stability batches. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

***Manufacture of the product and process controls***

The finished product manufacturing process consists of five main steps: dissolution of the active substance in WFI, pH adjustment, sterile filtration, aseptic filling and stoppering. The process is considered to be a non-standard manufacturing process.

The syringe barrels with staked needle and rigid needle shield are ready to use with no further treatment during the manufacturing process. Details on the sterilisation conditions for the plungers and the syringes were presented.

The filtration process is sufficiently well described in the dossier. The dossier states the equilibration time of the active substance at room temperature and all intended and validated hold times.

The applicant performed a risk assessment exercise utilizing risk priority indices which are calculated considering severity, probability and detectability of the respective risk of a manufacturing process parameter. The applicant explains that based on the calculation of the risk priority indices after implemented risk mitigation steps and planned validation, no process steps were identified to be critical. This approach is not in line with the definition of a critical process parameter in ICHQ8 (R2). Monitoring or controlling a process parameter does not change its criticality, the process parameter remains critical but well controlled. The applicant updated process parameters in the dossier. This was considered to be acceptable.

As the original dossier contained only process validation protocols for the proposed batches sizes, a major objection was raised requiring process validation data to be submitted for this non-standard manufacturing process (i.e. aseptic processing and sterile filtration).

The applicant presented a validation report for the finished product manufacturing process for three batches at a nominal batch size. The dossier also contains results of media fill runs, which are considered acceptable. Information on autoclave sterilisation of components, equipment parts and production materials, filling-line sterilisation validation and environmental monitoring are included.

The applicant's conclusion that the validation data for the provided batch size is also representative for a larger batch size without further supporting data was not accepted. Therefore, the larger batch size has been deleted from module 3. The Major Objection was considered to be resolved by the provision of process validation data and removal of the larger batch size from the dossier.

***Product specification***

The finished product specifications include appropriate tests for this kind of product/dosage form; appearance (visual), identification by duplex retention time (IPRP-HPLC), identification (IR), deliverable dose (Ph. Eur.), uniformity of dosage units (Ph. Eur.), assay (UV), purity (non-denaturing IPRP-HPLC, denaturing AX-HPLC, denaturing IPRP-HPLC), pH (Ph. Eur.), osmolality (Ph. Eur.), elemental impurities (ICP-MS), sub-visible particles (Ph. Eur.), sterility (Ph. Eur.), gliding force and break loose force (ISO 11040-8), bacterial endotoxins (Ph. Eur.) and container closure integrity test (USP).

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

There are no significant differences between the impurity profiles of the finished product and the active substance, and no significant degradation of the finished product was observed during manufacturing or on stability storage at both long term and accelerated conditions. As purity is mainly controlled by the active substance manufacturing process, the finished product purity limits are mainly the same as for the active substance. The proposed acceptance criteria in the finished product specification for purity are accepted considering the limited available manufacturing and batch data. The applicant commits to re-evaluate the finished product specification limits, together with the active substance purity specification limits, when data from a sufficient number of additional commercial finished product batches will be available (REC4).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The identification methods are specific and can distinguish inclisiran from comparable active substances. The applicant commits to include testing for colour and clarity of the solutions based on Ph. Eur. 2.2.1. and Ph. Eur. 2.2.2. in the release and shelf-life specification after a sufficient number of batch data is generated (REC5).

A risk evaluation concerning the presence of nitrosamines was missing and resulted in a major objection. The applicant has provided a risk evaluation concerning the presence of nitrosamine impurities in the finished product applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)". The conclusions drawn by the applicant are acceptable. There is no risk of nitrosamines contamination.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated method was provided, demonstrating that all elemental impurity values were below 30% of the conservative PDE acceptance criteria. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Batch analysis data, including the results for the validation batches of finished product were provided. All results are within acceptance criteria and batch to batch consistency is demonstrated.

***Stability of the product***

Stability data from batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging (syringes) proposed for marketing.

The applied tests are those included in the shelf-life specification. All results were well within specification limits with no obvious trends observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrated that the finished product is not susceptible to light exposure.

Based on available stability data, the proposed shelf-life of 2 years with the special storage conditions *"This medicinal product does not require any special storage condition. Do not freeze."* as stated in the SmPC (section 6.3) are acceptable.

***Adventitious agents***

There is no risk of potential contamination with adventitious agents of viral or non-viral origin. The finished product, including the active substance and all excipients, does not contain any materials of human or animal origin.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Major objections raised relating to finished product process validation and requesting a risk assessment for possible nitrosamines impurities have been resolved (no risk for nitrosamines identified). There are five quality recommendations to update starting material, intermediate, active substance and finished product specifications when further commercial batch data is available.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## 2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should re-evaluate and tighten the specification limits of the phosphoramidite starting materials when data from a sufficient number of commercial active substance batches (additional 18 batches) will be available.
2. The applicant should re-evaluate and tighten the specification limits for the single strand intermediates when data from a sufficient number of commercial active substance batches (additional 18 batches) will be available.
3. The applicant should re-evaluate and tighten the active substance specification limits when data from a sufficient number of commercial active substance batches (additional 18 batches) will be available.
4. The applicant should re-evaluate and tighten the finished product specification limits when data from commercial finished product batches will be available in which the additional 18 batches of active substance are used. Revised finished product specifications should be provided together with the revised active substance specification.

5. The applicant should introduce colour and clarity of the solutions test based on Ph. Eur. 2.2.1. and Ph. Eur. 2.2.2. in the release and shelf-life finished product specification at the same time when re-evaluation of the finished product specification limits is conducted.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

Inclisiran (also referred to as ALN-PCCSSC) is a double stranded small-interfering RNA (siRNA) molecule, the antisense strand of which is modelled to specifically correspond to human Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) mRNA. PCSK9 protein is predominantly expressed by the liver and is critical for the down regulation of hepatocyte low density lipoprotein receptor (LDLR) expression, which results in a subsequent reduction of circulating low density lipoprotein cholesterol (LDLC).

Inclisiran was developed as an adjunct to maximally tolerated statin therapy. Inclisiran is administered subcutaneously (SC) by a health care provider initially, again at 3 months, and then every 6 months as 300 mg inclisiran sodium injection.

The pharmacology, safety pharmacology, pharmacokinetics, and toxicology of inclisiran were evaluated in a series of in vitro and in vivo nonclinical studies. The nonclinical testing strategy for inclisiran was consistent with existing regulatory guidance. All pivotal studies were conducted in accordance with the Good Laboratory Practice (GLP). There are some deviations in the non-clinical development program as summarized in the Table below.

**Table 1.1: Justifications and assessment of the justifications of missing data**

| Absent data | Justification | Assessment |
|---|---|---|
| *4.2.1.4 Pharmacodynamic Drug Interactions* | *In vivo drug drug interaction (DDI) studies were not conducted because there is a low likelihood of inclisiran impacting DDI. Inclisiran does not exhibit direct or time-dependent inhibitory potential towards seven human cytochrome P450 isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5), and inclisiran does not induce human CYP1A2, CYP2B6 and CYP3A4. In addition, inclisiran does not act as a substrate or inhibitor of human transport proteins including MDR1, BCRP, OAT1, OAT3, OCT1, OCT2, OCT3, OATP1B1, OATP1B3, MATE1, MATE2k, and BSEP. In addition, because inclisiran will be co-administered with statins in the clinic, a GLP toxicology study was conducted to evaluate the potential toxicity of combined administration of inclisiran and atorvastatin to Cynomolgus monkeys for up to 85 days. This study did not reveal any new or exacerbated toxicities or impact on toxicokinetics associated with coadministration of inclisiran and atorvastatin compared with administration of each compound alone.* | There is an issue regarding pharmacodynamic drug-drug interactions. Additional studies are currently not considered necessary. |
| *4.2.3.1 Single-Dose Toxicity* | *This was considered to be scientifically justified as repeat dose toxicity studies in the rat and monkey were conducted using intermittent dosing schedules (once every week, once every 2 weeks or once every month) providing sufficient safety data to guide first-in-human studies and clinical dose selection.* | The applicant´s view is agreed to. |
| *4.2.3.5.4 Off spring /juvenile* | *In accordance with EMA advice, a juvenile toxicology study was not conducted since it was unlikely to generate additional information from what is already available [CHMP Scientific Advice 2017]* | The applicant´s view is agreed to. |

| | | |
|---|---|---|
| 4.*2.3.6 Local Tolerance* | *Dedicated local tolerance studies have not been conducted. Detailed analysis of the injection site using modified Draize scoring as well as macroscopic and microscopic analysis were included in the pivotal GLP toxicology studies in Sprague-Dawley rats and Cynomolgus monkeys.* | The applicant´s view is agreed to. Dedicated local tolerance studies are not considered necessary. |

## 2.3.2. Pharmacology

### *Primary pharmacodynamic studies*

Inclisiran is a double stranded chemically synthesised small-interfering RNA (siRNA) molecule, the antisense strand of which is modelled to specifically correspond to human Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) mRNA. PCSK9 protein is predominantly expressed by the liver and is critical for the down regulation of hepatocyte low density lipoprotein receptor (LDLR) expression.

The applicant conducted data mining analysis and directed sample analysis that showed there are no naturally occurring polymorphisms in the target sequence of inclisiran, and therefore no reduction of activity is anticipated for patients from any ethnic background. The applicant states that the nucleotide sequence of inclisiran exhibits complete homology to the analogous sequences in the human and Cynomolgus monkey PCSK9 genes and partial homology to the rat and mouse PCSK9 gene sequences. Consequently, the evaluation of the in vivo pharmacological activity of inclisiran that guided the clinical development program was primarily conducted in monkeys. In response to a request, the applicant explained in a detailed manner the extent of identity between the antisense strand of inclisiran and the respective regions of rat, mouse and rabbit PCSK9 mRNA sequence. For the rat and for the mouse, 100 % complementarity was shown for the seed region and partial homology for the remainder. One mismatch was detected for the seed region and 3 mismatches in the remaining region for the rabbit. Sequence homology was sufficient to result in pharmacologic activity (LDL-C decreases) of inclisiran in all three species. Reproductive toxicity of inclisiran was studied in rats and rabbits. Therefore, it is agreed that the relevance of the species chosen for the assessment of pharmacologic and toxicological effects has been shown and that rat and rabbit were adequate animal species for reproductive toxicity studies with inclisiran.

Inclisiran consists of chemically modified (2´-Fluoro-, 2'O-Methyl-) nucleotides (except one thymidine) with several phosphorathioate-linkages at/close to the ends of both strands (5'- and 3'-ends of antisense strand; 5'-end of sense strand) and a triantennary N-Acetylgalactosamine (GalNAc) covalently linked to the 3'-end of the sense strand to target the molecule to hepatocytotic uptake via asialoglycoprotein receptors (ASGPR). The ASGPR is a member of the C-type lectin family of receptors that recognizes and binds glycoproteins with terminal galactose (Gal) or GalNAc residues. It is expressed on the cell surface of hepatocytes at a high copy number (0.5-1 million per cell) and facilitates clearance of desialylated glycoproteins from the blood through endocytosis. According to the proposed mechanism inclisiran uptake through ASGPR on hepatocytes leads to receptor-mediated endocytosis followed by release of inclisiran from the endosome into the cytoplasm and recycling of the ASGPR back to the cell surface for successive rounds of uptake. The applicant confirmed that the asialoglycoprotein receptor (ASGPR) delivery system is not expected to be saturated, as, based on an

animal's PK data analysis provided by the applicant, a saturation of liver ASPGR was not observed in rasH2 wild type mice, rats and monkeys.

In hepatocytes, the antisense strand is incorporated in the RNA-induced silencing complex (RISC) and directs catalytic breakdown of mRNA for PCSK9 thereby inhibiting translation of PCSK9 protein. A single siRNA-bound RISC has an enzymatic activity and cleaves many transcripts and the duration of action may be longer than other mechanisms.

In HeLa or Hep3B cells inclisiran delivered via transfection into the cells (and not entering cells via cell surface asialoglycoprotein receptors) inhibited PCSK9 synthesis with an $IC_{50}$ value in the picomolar range.

When inclisiran was injected once SC in transgenic mice expressing human PCSK9 (hPCSK9) 10 days post injection hPCSK9 serum levels were lowered dose-related with an $ED_{50}$ of 2 mg/kg bw. and $ED_{80}$ = 6 mg/kg bw.

After single SC dosing inclisiran exhibited in female Cynomolgus monkeys a dose-dependent and sustainable reduction of PCSK9 protein paralleled by a lowering of serum LDL-C with similar kinetics. No PD effect was observed at 0.1 and 0.3 mg/kg bw. A pronounced PD effect on PCSK9 and LDL-C levels was observed at doses of 3 mg/kg bw and higher (6 mg/kg bw and 10 mg/kg bw) with no difference in time to nadir (approx. Day 20 post dose). At doses of 6 mg/kg bw or 10 mg/kg bw mean maximal PCSK9 reductions of about 85% and LDL-C lowering of about 68% were recorded. A dose dependent effect on the duration of PCSK9 and LDL-C reduction was observed with PCSK9 and LDL-C levels returning to baseline at approximately Day 130 and Day 100 post dose in the 3 mg/kg bw and 6 mg/kg bw groups, respectively, and remaining below baseline through Day 180 post dose in the 10 mg/kg bw group.

In another study in female Cynomolgus monkeys several SC multi-dose regimen following an initial administration of 6 mg/kg bw of inclisiran were investigated. Monthly (QM) dosing regimens of 1 mg/kg bw of inclisiran or higher were successful at maintaining the levels of PCSK9 and LDL-C reduction achieved after the initial 6 mg/kg bw dose for up to one year whereas with SC administration of 10 mg/kg bw every 3 months (quarterly; Q3M) partial recovery of PCSK9 and LDL-C levels were observed prior to administration of the next quarterly dose.

In yet another study in female Cynomolgus monkeys with single IV administration of 6 mg/kg bw of inclisiran, single SC administration of 1,3, and 6 mg/kg bw of inclisiran, and single SC administration of 6 mg/kg bw of inclisiran followed by multiple monthly (4 times) or biweekly (7 times) SC administrations of 3 mg/kg bw of inclisiran pharmacodynamics and pharmacokinetics were investigated. PCSK9 protein levels were maintained at ≥ 50% of baseline for 7 days, 28 days and 84 days following single dose SC administration of 1 mg/kg, 3 mg/kg and 6 mg/kg, respectively, and for 84 days following the last dose in the groups receiving biweekly or monthly injections. Reductions of LDL-C levels below 50% of baseline were sustained for 49 and 56 days following the last monthly and biweekly dose, respectively. The plasma levels of inclisiran were below the lower limit of quantitation (20 ng/mL) in all dose groups by 24 hours post dose indicating a temporal disconnect between inclisiran PK and PD effects.

Chain-shortened metabolites of inclisiran were observed in *in vitro* and *in vivo* metabolic profiling. In response to a request, the applicant clarified that while minor amounts of extensively truncated metabolites and metabolites resulting from endonuclease cleavage are not expected to enter the RISC and, therefore, produce any off-target effect, n-1 and ´n-2 metabolites and metabolites resulting from truncation on the 5´end up to n-4 do exhibit similar activity as the unmetabolised parent strand. It is assumed, that inclisiran treatment does not result in any adverse effects related to off-target activities based on the long-term toxicology studies in rats and monkeys.

The PD activity of inclisiran including reduction of endogenous plasma PCSK9 and serum LDL-C levels was determined following single and multiple SC dose administration to cynomolgus monkeys and transgenic mice. In response to a request, the applicant clarified that *in vivo* studies in animal disease models of hypercholesterolemia would be of minimal impact to the understanding of inclisiran's biology and pharmacology in human. The argumentation included among others the facts that use of PCSK9 antibodies in clinical practice has validated PCSK9 as a pharmacologic target for reducing LDL-C and that there are species differences in cholesterol fractions.

## *Secondary pharmacodynamic studies*

Regarding possible off-target activity a bioinformatic analysis was used to identify a set of transcripts that may potentially be inhibited by the antisense strand of inclisiran based on sequence homology. Specificity was predicted for the 19-mer core sequence by performing a comprehensive search against the human transcriptome. Twenty potential off-target transcripts were assayed using quantitative PCR in Hep3b cells transfected with inclisiran. Two targets were not expressed in Hep3b cells. Inclisiran did not substantially inhibit expression for any of the other 18 potential off-targets that were tested in this assay with a factor of ≥45-fold between the "on-target" suppression of PCSK9 by inclisiran and the "off-target" suppression of any of the predicted off-target transcripts and no $IC_{50}$ values could be determined. The off-target transcript inhibition was considered low, even at high inclisiran concentrations. In response to a request, the applicant provided appropriate data on the 20 off-target genes identified whose expression may be impacted by inclisiran in order to explain that none are thought to be housekeeping genes and to clarify that no impact on the cell hemostasis is expected.

The applicant substantiated that due to position and extensive number of 2'-O-Methyl modifications as well as the addition of the GalNAc ligand to the 3' end of the sense strand of inclisiran the likelihood that the sense strand would lead to 'off-target` transcript suppression is significantly decreased. Even after removal of the GalNac residue,RNAi activity of the sense strand is not expected.

## *Safety pharmacology programme*

The applicant conducted a cardiovascular and respiratory safety study in conscious telemetered male Cynomolgus monkeys with SC injections of up to 250 mg/kg bw of inclisiran. Neither statistically significant effects on PR, QT or QTc intervals, or QRS duration, nor abnormal ECG waveforms or arrhythmias were attributed to administration of inclisiran. In addition, no effects on heart rate, systolic, diastolic, mean arterial, pulse pressures or respiration rate was attributable to administration of inclisiran. The applicant clarified that no other measurements of respiratory function apart from the determination of respiratory rate were collected neither in study 8297017 nor in any other nonclinical studies. As inclisiran has meanwhile been used and investigated in humans in clinical trials, it is not considered appropriate to request the conduct of a new non-clinical study investigating another respiratory parameter apart from respiratory rate in animals. The safety factor of 67 resulting with the highest dose investigated (250 mg/kg bw) between the experimentally achieved $C_{max}$ and the clinically intended therapeutic $C_{max}$ in humans at the 300 mg dose is considered sufficient. The molecular weight of inclisiran (free acid) is high (16339.53 g/mol). No *in vitro* cardiac ion channel assays were performed. The electrocardiographic effects of inclisiran at a supra-therapeutic dose (900 mg) was investigated in a Phase 1 clinical study ([ORION-12]). In that study, inclisiran did not produce clinically or statistically significant electrocardiographic effects, including prolongation of QTcF.

Neurological evaluations were incorporated into the repeat dose toxicology studies conducted in Cynomolgus monkeys. In the 40 week repeated dose toxicology study the parameters analysed included postural reactions (proprioceptive positioning, placing reactions), spinal nerve function

(muscle tone, withdrawal and perineal reflex), and cranial nerve effects (head movement, head symmetry, head muscle tone, and jaw tone, eye reactions, eye symmetry, eye position, palpebral reflex, and pupil light reflex). There were no inclisiran-related effects reported on any parameter up to the highest doses tested and the NOEL for neurological effects was ≥ 300 mg/kg, the highest dose tested in the 40 week study.

### *Pharmacodynamic drug interactions*

Dedicated PD drug interaction studies have not been conducted in animals but the applicant performed a 13-week repeated dose toxicology study in Cynomolgus monkeys with co-administration of inclisiran (once monthly SC) and/or atorvastatin (orally daily) in which PCSK9 levels and lipid profiles where investigated. The study did not reveal any marked differences in PD parameters associated with administration of the combination of inclisiran or atorvastatin compared to administration of either inclisiran or atorvastatin alone. All groups receiving inclisiran (with or without atorvastatin) except females receiving 300 mg/kg bw of inclisiran alone, showed moderate decreases in triglyceride levels, whereas atorvastatin alone did not exhibit an effect on triglyceride levels. The difference in response from the male cohort may be due to experimental and/or individual animal variability, as the triglyceride values were within a reference interval for cynomolgus monkeys (Koga et al 2005). It should be noted that inclisiran did not produce reductions in serum triglycerides in monkeys in the 4-week ([8302575]), 15-week ([8297016]) or 40-week ([5001352]) pivotal toxicity studies. The majority of the data indicate that inclisiran alone does not reduce serum triglycerides in monkeys.

## 2.3.3. Pharmacokinetics

The pharmacokinetics of inclisiran were investigated by the applicant in rodent and non-rodent species and *in vitro* using human tissue.

The applicant used a variety of bio-analytical methods to investigate the pharmacokinetics of inclisiran and its short-chain oligonucleotide metabolites. The validation of the bioanalytical methods included the linearity, sensitivity, accuracy, precision, dilution, selectivity, recovery, matrix effect, and carryover. In all cases, validation did not include incurred sample reanalysis (ISR) but ISR was conducted in study [8302576] titled "ALN-PCSSC: A 4-Week Repeat-Dose Toxicity and Toxicokinetics Study in Rats with an 8-Week Recovery" and Study [8302575] titled "ALN-PCSSC: A 4-Week Repeat Dose Toxicity and Toxicokinetics Study in Cynomolgus Monkeys with an 8-Week Recovery Phase", which is considered acceptable. For the LC-TOF-MS assay the standard curve was constructed based on the duplex with two separate calibration curves constructed one for the AS and one for the sense strand. The AS strand was typically present at lower concentrations than the sense strand, which is considered being due to the sense strand being more stable due to the GalNAc group at the 3' end which has steric effects that unlike the AS strand protects the 3' end from exonuclease metabolism.

Systemic bioavailability of inclisiran after SC administration of 5 mg /kg bw was determined in the rat as being 35.1% (compared to IV bolus injection) to 48.9% (compared to IV infusion). In the monkey a systemic bioavailability after SC administration of 24.7% to 33.8% was demonstrated (depending on the concentration of the SC administered formulation). The long half-life of inclisiran at the SC dose site (~526 hours in rats) based on a radiolabelled study could explain the apparently low absolute bioavailability of the SC route.

A $T_{max}$ of 1 to 2 hours after SC administration was determined in both species. There were no gender differences identified in PK parameters. In the range between SC administration of inclisiran at 1 and 5

or 6 mg/kg bw $C_{max}$ and AUC increased dose-proportionally in both species. After single SC administration of 5 mg/kg inclisiran to rats $C_{max}$ values between 592 ng/mL to 787 ng/mL were determined. Pharmacokinetic parameters after the last dose of repeated administration in biweekly or monthly intervals were very similar to those after single administration in both species. Inclisiran plasma $t_{1/2}$ ranged in the rat from 0.9 to 1.7 hours and in the monkey from 1.9 to 4.3 hours after SC administration.

The degree of plasma protein binding increased as the inclisiran concentrations decreased, with the highest degree of binding observed at the lowest concentration tested for all species including mouse, rat, monkey, and human plasma. At 0.5 µg/mL (human $C_{max}$ = 0.507 µg/mL), the lowest concentration of inclisiran assayed, plasma protein binding was similar between species and ranged from 87.4% for human plasma to 93.1% for rat plasma.

Tissue distribution after SC administration was investigated in rats and Cynomolgus monkeys in selected organs using unlabelled inclisiran (1, 5 or 25 mg/kg bw for the rat; 1, 3 or 6 mg/kg bw for the monkey) and in many organs using $^{14}C$ labelled inclisiran (65 mg/kg bw for the rat; 20 mg/kg bw for the monkey). In general $C_{max}$ and AUC of liver and kidney are by far higher than those ones of plasma.

The study using unlabelled inclisiran in the rat showed that inclisiran was measurable in the liver and kidney to at least 336 hours (= 14 days) and 1344 hours (= 56 days) post dose, respectively, after a single dose. Liver $C_{max}$ and $AUC_{0-t}$ values generally increased in a dose proportional manner over the range evaluated. Mean apparent liver half-lives ranged from 53.1 to 191 hours across SC doses. Mean kidney concentrations were lower by approximately 2-5 fold than liver at all dose levels. Kidney $C_{max}$ and $AUC_{0-t}$ exposure increased in a dose proportional manner between 1 mg/kg bw and 5 mg/kg bw and greater than dose proportional manner between 5 mg/kg bw and 25 mg/kg bw. Mean apparent kidney half-lives ranged from 244 hours to 355 hours across the SC doses. The tissue distribution of inclisiran following a single SC dose of 5 mg/kg bw indicates that inclisiran is predominantly localized in the liver followed by kidney. Markedly lower inclisiran exposure based on $AUC_{0-t}$ was observed in adrenal (1076 fold lower), thymus (758 fold lower), thyroid (93 fold lower), pancreas (36 fold lower), jejunum (278 fold lower) and testis (743 fold lower) compared to liver. Inclisiran was no detected in the brain (LLOQ = 160 ng/g).

The study using $^{14}C$ labelled inclisiran in the rat showed that the site of SC administration showed the by far highest $C_{max}$ and AUC values. In response to a request, the applicant clarified that the highest concentrations of radioactivity at the injection site are due to the concentrated radioactive dose administered and are not a species specific effect. Nevertheless, in all non-clinical studies inclisiran was well tolerated at the injection sites.

Ten times lower $C_{max}$ and AUC values compared to the injection site were found in the liver and similar or slightly lower values in the kidney. All other organs showed $C_{max}$ values by a factor of at least 20 or AUC values by a factor of at least 8 times lower than shown for the kidney. Elimination of radioactivity from all tissues was relatively slow and half-life values, if determinable, were in all organs at least 150 hours, with 526 hours at the injection site, 270 hours in the liver and 360 hours in the kidney. Relatively long, reliable, tissue half-life values (> 500 hours) were observed in brain (medulla, 1105.9 hours), eye (uvea, 1070.8 hours), adrenal gland (725.2 hours), spleen (606.7 hours), spinal cord (553.1 hours), and stomach (gastric mucosa, 531.6 hours).

In the study using unlabelled inclisiran in the monkey with a single IV dose of 6 mg/kg or single SC doses of 1, 3 and 6 mg/kg or a loading SC dose of 6 mg/kg followed by three administrations of 3.0 mg/kg monthly (QM) or six administrations of 3.0 mg/kg biweekly (Q2W) inclisiran was not detected in kidney and heart tissue with any dose regimen. Inclisiran was detectable in liver in all dose regimens, but only at the 8 hour post dose time point. At 8 hours post dose, the liver concentrations after SC administration of 6 mg/kg were approximately 16 fold higher than those after an IV administration of 6

mg/kg. It should be noted that inclisiran was detectable in liver, kidney and heart samples collected from cynomolgus monkeys in the pivotal toxicology studies in which higher doses were administered. Regarding investigation of inclisiran liver tissue concentration, animals underwent obviously multiple times liver biopsy sampling. The reasoning for multiple sampling in the same animal was to save the number of monkeys used in this experiment performed rather early in drug development.

The study using 20 mg/kg bw of $^{14}C$ labelled inclisiran in the monkey the injection site was not investigated but qualitative whol- body autoradiographs performed in monkeys showed high levels of radioactivity at the injection site. Liver and kidney were the organs with the highest $C_{max}$ and AUC values with the $C_{max}$ values being similar and the AUC value for the liver being 20 to 30 times higher than that one of the kidney. The organ with the third highest exposure were found to be lymph nodes (about 5 times lower $C_{max}$ than for the liver). For the liver a half-life of about 2,000 hours was calculated, for the kidney a half-life of about 10,000 hours. For cardiac blood the long half-life of 672 hrs was calculated. In response to a request, the applicant ascribes this long value to the high sensitivity of LSC. A significant drop in radioactivity was seen around 24 hours, and low levels of radioactivity in cardiac blood were detected up to 1008 hours. When the calculation of cardiac blood half-life is based on the time points between 4 and 24 hours only, a half-life of about 3.6 hrs is obtained which is more in line with values obtained using unlabeled inclisiran. The applicant has discussed possible effects of the high and long-lasting concentration of inclisiran as determined in livers and kidneys of monkeys. Slight increases in enzymatic markers (e.g. ALT) were seen but it is agreed that these slight changes were not considered adverse. Slight enzymatic changes were also reported in humans, but no overt liver or kidney toxicity was seen in humans.

Inclisiran was stable when incubated in pooled serum obtained from mouse, rat, monkey, and human. Following 24 h incubation of inclisiran in mouse, rat, monkey, and human serum at 37°C, the percent of antisense strand remaining was approximately 85%, 82%, 72%, and 80%, respectively; the percent of sense strand remaining was approximately 95%, 91%, 91%, and 87%, respectively.

Metabolism of inclisiran in rats and monkeys has been studied using unlabelled and $^{14}C$-labelled inclisiran. Inclisiran appears to be metabolised only to a limited extent. In both species the AS strand metabolites formed mainly from sequential exonuclease activity on the 5′ and 3′ ends.

Using unlabelled inclisiran after SC administration parent substance and/or metabolites were detected in plasma from rats and monkeys at 0.5, 2, 8 and 24 hours (only for the monkey). For the sense strand only the parent strand or the parent strand with loss of one to three sugars could be detected in both species at the mentioned time points. Regarding the AS strand in both species only the parent strand or the parent strand with likely a 5´ end deletion of one nucleotide was detected with the exception of a minor amount (8%) of a 3´end truncation by 7 nucleotides at the time point of 2 hours in the monkey. Regarding formation of metabolites in the liver of rats and monkeys for both species only data obtained 8 hours after SC administration are available. Concerning later time points, data obtained at 72 hours for the monkey and 96 hours for the rat are available. With regard to the sense strand at the investigated time points, truncations only targeting the sugar moieties are the by far most prominent entity of metabolites yielding between 82 to 100% of total identified metabolites. Regarding the AS strand at 8 hours parent and by one nucleotide from the 3´end truncated AS strand constitute at least 97% of the detected antisense material. The same holds true at the 96 hours for the rat. In monkey liver at 72 hours parent and by one nucleotide from the 3´-end truncated antisense strand on the one hand side and by 6 or 7 nucleotides 5´end truncated metabolites with or without a one nucleotide 3´end truncation on the other hand side constitute both approximately half of the identified antisense material.

Based on studies using $^{14}C$-labelled inclisiran AS(n-1) was determined to be the only metabolite consistently detected and quantifiable in all matrices investigated (plasma, urine, bile [only rat],

faeces, liver, kidney, injection site [only rat]), although at markedly lower concentrations than the AS parent strand. As 5´ and 3´ end of the AS strand share the same terminal bases, a distinction between both ends could not be made. In rats and monkeys, based on their respective $C_{max}$ concentrations, AS(n-1) was 27.5-fold and 24-fold lower in plasma, respectively, and 35.1-fold and 9.5-fold lower in liver, respectively, and 62.4-fold and 13.7-fold lower in kidney, respectively, than the parent AS strand. The AS(n-2) metabolites were only detected in the urine from rats and urine and liver from monkeys, and at levels only slightly above the limits of quantitation. The other AS strand metabolites were not present in high quantities and encompassed a minor portion of the entire profile.

The S strand of inclisiran is also not extensively metabolised. The major S strand metabolites in both species resulted from the sequential loss of the three GalNAc groups on the 3' end, followed by the loss of their three associated linker groups. There were additional minor metabolites formed from successive loss of nucleotide groups from the 3'end and there is evidence for minor metabolism from the 5`end.

Renal excretion is the primary route of elimination with approximately 29% and 32% of the administered dose of inclisiran recovered in the urine of rats and monkeys, respectively, over a 7-day period with most of the amounts being excreted during the first 24 hours. Over the 7-day period in the rat 23% of the total dose were excreted via faeces, whereas only 1.6% were recovered from faeces in monkeys. The amount of radioactivity remaining in the carcasses of rats was determined after 96 hours and was approximately 39%. This correlates well with the long tissue retention time of inclisiran in tissues.

Excretion of inclisiran to milk was observed in the F0 generation of rats dams. High inter-animal variability was observed in maternal milk data: overall, maternal mean plasma concentrations increased with increasing dose levels between 50 and 150 mg/kg/day; and the mean milk concentrations increased with increasing dose levels between 50 and 100 mg/kg/day, and the mean concentrations between 100 and 150 mg/kg/day were generally comparable. The inclisiran concentrations were generally lower in milk compared to maternal plasma at 100 and 150 mg/kg/day dose levels. At 50 mg/kg/day, no conclusion could be made regarding milk to plasma ratios due to inter-animal variability in milk and maternal plasma data.

Inclisiran does not exhibit direct or time-dependent inhibitory potential towards seven human cytochrome P450 isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5), and inclisiran does not induce human CYP1A2, CYP2B6 and CYP3A4. In addition, inclisiran does not act as a substrate or inhibitor of human transport proteins including MDR1, BCRP, OAT1, OAT3, OCT1, OCT2, OCT3, OATP1B1, OATP1B3, MATE1, MATE2k, and BSEP.

## 2.3.4. Toxicology

### *Single dose toxicity*

Toxicity studies were performed in mice, rat, rabbit and monkey. The choice of species is considered adequate.

Single dose toxicity studies were not conducted. This approach is in line with the current view is that adequate information can be obtained from other sources than specific single dose toxicity studies (EMA/CHMP/SWP/81714/2010).

## *Repeat dose toxicity*

Repeated dose toxicity studies were performed in mice rats, rats and Cynomolgus monkeys. Three non-GLP compliant studies have been performed; one in male and female CD mice, one in male and female SD rats and one in male Cynomolgus monkeys. Inclisiran was administered subcutaneously once weekly for 4 weeks (5 doses in total) at doses of 0, 30, 100 and 300 mg/kg. Studies were accompanied by evaluation of toxicokinetics.

There was no overt toxicity in these studies. The main findings were limited to disturbances in the lipid profile (decrease of LDL and cholesterol, to a lesser extend of HDL) which can most likely be attributed to the pharmacodynamic activity of inclisiran and some minor effects on liver (rat: deposits of neutral lipids; vacuolation in the highest dose group,), kidney (monkey: basophilic granules, rat: basophilic pigment, tubule; chronic progressive nephropathy, mineralisation, focal) and heart (minimal mononuclear cell infiltrate).

GLP compliant studies were performed in rats and Cynomolgus monkeys. The studies were accompanied by toxicokinetic investigations.

Three studies with a dosing phase of 4, 15 and 29 weeks were performed in rats. Inclisiran solved in saline was administered subcutaneously in a dose volume of 1.25 ml/kg in a variable dosing scheme into different predefined injection sites. In the 4-week study male and female animals received 0, 10, 50, 250 mg/kg inclisiran every two weeks (=3 doses) or 10 mg/kg once weekly (= 5 doses). The recovery period was 8 weeks. The 4-week rat study (8302576) suffers several inaccuracies which can be traced back to inaccuracies in animal identification and group assignment and unplanned cohabitation. However, in the study program there are toxicity studies in rats of longer duration. The overall impact for marketing authorization appears therefore rather low.

In the 15 weeks study male and female animals received 0, 10, 50, 250 mg/kg once monthly (=4 doses) or 25 mg/kg (=8 doses) every two weeks. The recovery period was 8 weeks.

In the 29 weeks study male and female rats received, 10, 50, 250 mg/kg once monthly (=8 doses). The recovery phase was 13 weeks.

Three studies with a dosing phase of 4, 15 and 40 weeks were performed in Cynomolgus monkeys. Inclisiran solved in saline was administered subcutaneously in a dose volume of 1.25 ml/kg (4 and 15 weeks) or in a dose volume of 1.5 ml/kg (40 weeks) in a variable dosing scheme into different predefined injection sites. In the 4 weeks study male and female animals received 0, 10, 50, 250 mg/kg every two weeks (=3 doses) or 30 mg/kg once weekly (=5 doses). The recovery phase was 8 weeks.

In the 15 weeks study male and female animals received 0, 10, 50 250 mg/ kg once monthly (= 4 doses) or 125 mg/kg every two weeks (=8 doses). The recovery was 15 weeks.

In the 40 weeks study male and female animals received 0, 30, 100, 300 mg/kg once monthly (=11 dose). The recovery was 13 weeks.

All animals were investigated during the study course and at the end of the respective study for usual toxicological endpoints. Studies in monkeys were widened by investigations on PCSK, Anti-Drug Antibody (ADA) analysis, biomarkers (troponin I, DHEA, DHT) and T-cell dependent antibody response (TDAR/ IgM and IgG).

In the 4, 15 and 29-week toxicology studies in rats, minimal to marked vacuolation was noted in hepatocytes of males and/or females in most dose groups. The vacuolation was characterised by microvesicular (numerous small vacuoles without nuclear displacement) and/or macrovesicular (a single large vacuole that displace the nucleus) types. Following the recovery periods in all three

studies, the liver hepatocyte vacuolation was still present but the extent of the finding was greatly reduced indicating a decrease in severity and partial recovery. Following the recovery phase minimal to mild randomly distributed foci of slightly hypertrophied hepatocytes cytoplasm and central hyperchromatic nuclei of the basophilic type was present in one female from the 50 mg/kg and three females from the 250 mg/kg dose groups. A finding was not observed during the main phase of this study. The applicant´s conclusion that the finding of hepatic foci of cellular alteration is of uncertain relevance, and the nonclinical data do not indicate a potential human risk for neoplasia was agreed to.

In the 4 week study in rats, basophilic granules considered minimal to slight were noted in the kidney tubule cell cytoplasm of animals in the 50 and 250 mg/kg dose groups, in the 15 week study, minimal to moderate basophilic granules were noted in the kidney tubular epithelium of animals in the 25, 50 and 250 mg/kg dose groups, and in the 29 week study these findings were present in the 50 and 250 mg/kg dose groups. In general, the basophilic material formed variably sized round vacuolated structures in the cytoplasm. Following the recovery periods in all three studies, the basophilic granules were characterised as minimal and limited to the 250 mg/kg dose groups. There were no microscopic kidney findings in the 4, 15 and 40-week monkey studies.

The 4, 15 and 40-week toxicology studies in monkeys were not associated with vacuolation in hepatocytes. However, in the 15 and 40-week studies there were findings of basophilic granules in hepatocyte cytoplasm of several animals encompassing all dose groups. In the 15-week study the severity ranged from minimal to slight and in the 40 week study the severity ranged from minimal to mild. Following the recovery periods, the basophilic staining was not present in the low dose group (50 mg/kg), indicating recovery, but still present in the mid (125 mg/kg) and high (250 mg/kg) dose groups in the 15 week study and present in all dose groups (30, 100, and 300 mg/kg) in the 40 week study, but with decreased incidence and severity indicating partial recovery.

The applicant points out that presence of vacuolation, particularly in the liver, and basophilic granules in the kidney were not associated with additional degenerative microscopic findings or consistent correlative changes in clinical pathology parameters including liver function enzymes and urinalysis parameters.

In addition, there were indications that these findings were reversible signifying that the vacuolation and basophilic granules are not adverse toxicological findings. The content of these vacuoles/ basophilic granules was not investigated further, but the applicant believes that this material is inclisiran, which accumulates within the cells. This explanation is considered acceptable.

A similar finding in the 4, 15 and 40-week studies in monkeys, was a minimal to moderate accumulation of vacuolated macrophages in the sinusoids of lymph nodes (mandibular, mesenteric, axillary, or inguinal) across all inclisiran dose groups. The macrophages were characterised by accumulations of foamy cytoplasmic vacuoles, with faintly basophilic staining often distending the cytoplasm. The finding was most common in the mesenteric and axillary lymph nodes. No dose relationship in severity was noted. Following the recovery periods, the vacuolated macrophages were still present but with decreased incidence and severity indicating partial recovery; however, following the recovery period in the 15 week study this finding was not present in the 10 mg/kg dose group indicating complete recovery at this dose. Considering the rather high tissue distribution of inclisiran into lymph nodes the basophilic material is most likely accumulated inclisiran.

The primary clinical pathology findings across all studies and dose groups were changes in lipid profiles that were expected based on the pharmacologic activity of inclisiran. Reductions in LDL were consistent across all dose groups in the 4, 15 and 29-week toxicology studies in rats and 4, 15 and 40-week studies in monkeys. In addition, reductions in HDL were noted in the 4 and 15-week studies in rats but not in the monkey studies. Lipid profiles returned to control values during the recover periods. In addition, there were minimal increases in ALP in the high dose groups in rats in the 4 and 29-week

studies and monkeys in the 4 and 40-week studies that returned to control values during the recovery periods. The applicant does not discuss that finding in detail but refers to the publication of Blom et al 1998, indicating that the plasmatic ALP increase may be explained by the occupation of the galactose receptor by inclisiran and a therefore decreased plasmatic ALP clearance. This explanation appears to be acceptable.

Neurological assessments were included in the pivotal repeat dose toxicology studies conducted in Cynomolgus monkeys. These involved evaluation of general behaviour and awareness, gait, postural reactions, and spinal and cranial nerves. There were no findings that were indicative of inclisiran related changes in CNS activity up to the highest doses tested. In addition, tissue distribution studies conducted with 14C-labelled inclisiran showed that the amount of inclisiran in the brain relatively low compared to the liver.

Pro-inflammatory properties were investigated in a non-GLP study in monkeys and mice. There were no changes in levels of C-reactive protein, complement, and proinflammatory cytokines monkeys. In mice inclisiran did not significantly alter the levels of several different cytokines including G-CSF, IL-6, IP-10, KC, MCP-1, and TNF-α.

Immunotoxicity was investigated in a 85 day toxicity study in Cynomolgus monkeys. In this study inclisiran did not affect the generation of a TDAR following immunisation with KLH during the dosing or recovery periods. Anti-KLH IgM and IgG antibody titres for primary and secondary responses in inclisiran treated animals in all dose groups were similar to vehicle controls. In addition, in the same study, immunophenotyping by flow cytometry analysis showed that inclisiran did not impact total numbers of T-lymphocytes (CD45+/CD3+), T-helper (Th) lymphocytes (CD45+/CD3+/CD4+), T-cytotoxic (Tc) lymphocytes (CD45+/CD3+/CD8+), B-lymphocytes (CD45+/CD3-/CD20+) and Natural Killer (NK) cells (CD45+/CD3-/CD16+).

A GLP toxicology study was conducted to evaluate the potential toxicity of combined inclisiran and atorvastatin administration to cynomolgus monkeys for up to 85 days. There were no new or exacerbated toxicities observed when inclisiran and atorvastatin were coadministered compared to either test article alone. All inclisiran-related observations in the presence or absence of atorvastatin were similar to those noted in repeat dose toxicity studies. The NOAEL was 300 mg/kg for inclisiran when given alone and in combination with 25 mg/kg/day atorvastatin. In line with the SmPC inclisiran is also indicated in combination with other lipid-lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated. The respective combinations were not tested in animals. However, clinically significant interactions are not expected since no interactions with the CYP 450 system or common drug transporters were evident and the distinct mode of action compared to other lipid lowering substances such as the recombinant human IgG monoclonal antibodies against PCSK9 (alirocumab and evolocumab) or ezetimibe.

Although inclisiran was quantifiable at low levels in heart tissue samples, it did not associate with RISC indicating that there is a low likelihood that inclisiran will influence gene expression in tissues that do not express PCSK9.

The calculated safety margins a based on the highest dose applied and are based on the NOAEL doses in the pivotal chronic toxicity studies. They are 99-fold and 101-fold based on $C_{max}$ and 48.9 fold and 99.6 fold based on AUC in rats and monkeys, respectively, compared to the 300 mg human clinical dose. These safety margins are based on exposures generated from studies of once monthly dosing. The applicant points out that these would cover considerably more frequent administrations than the recommended dosing regimen of 300 mg initially, again at 3 months, and then every 6 months. However, the dose regime induces a persistent reduction in the lipid profile, which equals continuous application as indicated in humans. Considering this aspect, the data supports the application of 11 injections, which would equal more than 4 years of clinical use.

## *Genotoxicity*

A standard battery of in vitro and in vivo genotoxicity tests has been performed with inclisiran. Inclisiran was negative in in vitro Ames tests, a chromosome aberration assay in human peripheral blood lymphocytes and in an in vivo micronucleus test performed in rats. Therefore, inclisiran is not considered to be genotoxic in vitro and in vivo.

## *Carcinogenicity*

Long- and short-term carcinogenicity studies with inclisiran have been performed in rats for 104 weeks and Tg-RasH2 mice for 26 weeks. In the rat study inclisiran was applied via the s.c. route at once monthly intervals up to 250 mg/kg. In the transgenic mice study inclisiran was applied via the s.c. route at once monthly intervals up to 1500 mg/kg. In the 2-year rat carcinogenicity study a significant increase of benign mammary fibroadenoma was noted in female rats in the 95 and 250 mg/kg dose groups. In addition, there was a statistically significant trend in mammary tumour combinations in females including mammary fibroadenoma in the 250 mg/kg dose group. As tumour incidences were small and in the range of published historical controls of the breeder, the rats were derived from, this is not a concern. Furthermore, no increase in tumour incidences was reported for the 40 mg/kg dose group (NOEL). Exposure at Day 197 in females was 25100 hr*ng/mL ($AUC_{last}$). This corresponds to a safety margin of 3-fold compared to single human dose of 300 mg (AUC: 8590 hr*ng/mL, pooled PK analysis of combined data from healthy individuals in clinical studies ORION-6 and ORION-7). It has to be noted that in patients inclisiran will be initially administered, again at 3 months, and then every 6 months, thus dosing frequency and long-term exposure to inclisiran in humans is much lower as in the rat carcinogenicity study. Furthermore, inclisiran was negative in the 26-weeks carcinogenicity study with transgenic Tg-RasH2 mice up to doses of 1500 mg/kg, which is >100-fold the anticipated human exposure.

Overall, based on the results of the 2-year rat and 6-month transgenic mice carcinogenicity studies, inclisiran is not considered to be carcinogenic and mice and rats and does not indicate a carcinogenic potential in humans.

## *Reproduction Toxicity*

A complete set of reproductive and development toxicity studies as requested by the respective guidelines (ICH M3(R2), ICH S5) was performed for inclisiran in rats and rabbits. The choice of species for reproductive toxicity studies is considered adequate.

Separate studies on male and female fertility were performed in rats with subcutaneous injection of inclisiran. The administration of inclisiran once every two weeks for 4 weeks to male rats with doses up to 250 mg/kg was not associated with paternal toxicity or effects on spermatogenesis, fertility or early embryonic development.

Inclisiran was administered to female rats once every four days at doses up to 250 mg/kg beginning 14 days prior to cohabitation and during mating, and then once daily at doses up to 150 mg/kg during gestation up to gestation day 7. Inclisiran treatment did not result in maternal toxicity or effects on female fertility or early embryonic development including ovarian and uterine parameters, oestrous cycles and maternal performance. The NOAEL for male and female fertility was thus established for each study at the highest dose level with exposure margins of **41, respectively 19-times** based on AUC at the recommended human therapeutic dose.

Studies on embryo-foetal development with daily s.c. administration of inclisiran were performed in rats and rabbits. There was no evidence of embryo-foetal toxicity, -lethality or teratogenicity up to the highest dose administered in rats (150 mg/kg) with an exposure margin **of 15-times** as well as in rabbits (150 mg/kg) with an exposure margin of **37-times** based on AUC at the recommended human therapeutic dose.

Maternal to foetal plasma ratios in the rat were at least more than 60-fold depending on the dose. No inclisiran was detected in pooled foetal liver samples from the rat. There were no antibodies present in maternal plasma samples from the rabbit.

Toxicokinetic data showed no accumulation of inclisiran after repeated administration in the pregnant rat and rabbit. In general, a dose proportional increase in exposure with increasing dose was observed for both species but for the lower dose levels in rats where a more than dose proportional increase was noticed. No gender differences in toxicokinetic parameters were observed between pregnant rats and male rats.

Administration of inclisiran by s.c. injection from gestation day 6 to lactation day 20 was well tolerated in F0 female rats with no evidence of maternal toxicity or effects on maternal performance up to a dose of 150 mg/kg/day. There were no effects on the development of the F1 generation, including survival, growth, physical and reflexological development, behaviour, and reproductive performance. Accordingly, the NOAEL for maternal toxicity, maternal performance and the development of the F1 generation was 150 mg/kg/day. Inclisiran was excreted into the milk of lactating rats with milk to plasma ratios of 0.4 to 1.8-times. F1 generation pup plasma levels were below LLOQ.

## *Toxicokinetic data*

Toxicokinetic analysis indicated that inclisiran had a relatively short plasma half-life ranging from 0.76 hours to 7.65 hours in rats and 1.8 hours to 16.5 hours (18.6 in females only) in monkeys. There were no gender differences in TK parameters. Exposure tended to increase in a dose proportional manner and there was no accumulation of inclisiran in plasma following repeat dosing. In a limited tissue analysis, inclisiran was found predominantly in the liver which is the target organ followed by the kidney which is the primary organ of elimination. Inclisiran was present at higher concentrations and exhibited a longer half-life in liver and kidney than plasma. There was a dose related increase in tissue exposure and there did not appear to be target organ (liver) saturation, even in mice administered inclisiran up to 1500 mg/kg. In the 15 and 40-week toxicology studies conducted in monkeys there were sporadic incidences of animals developing ADA at or near the end of the dosing periods. Five animals in the 15-week study and three animals in the 40 week study developed low titre ADA. Due to technical issues, the data set concerning the 40 weeks study is too limited to conclude on antibody formation and toxicokinetic parameters. However, there were no evidence for neutralising effects of these ADAs since no effect on PK (plasma or tissues) or PD (PCSK9 and lipid lowering) parameters were observed.

## *Local Tolerance*

Dedicated local tolerance studies have not been conducted. However, Draize scoring as well as macroscopic and microscopic analysis of injection sites were conducted in all pivotal toxicology studies conducted in rats and monkeys. The dosing scheme applied prevents recurrent injections at the same side. In general, inclisiran was well tolerated at the injection sites despite of the rather high inclisiran residues. There were sporadic instances of local erythema and oedema associated with discoloration that ranged from very slight to moderate in severity that were self-limiting and not present following the recovery periods. Injection site microscopic findings were present in rats in the 29-week study and

included minimal to moderate perivascular mononuclear cell infiltrates and/or haemorrhage in males and females at ≥ 50 mg/kg. There was near compete resolution of these findings following the recovery period. There were no injection site microscopic findings in the monkey studies. Provided that the various injection sides will be used in clinical practice no overt local effects are expected.

### *Other toxicity studies*

The absence of dedicated impurity studies is adequately justified. Impurities can be considered qualified based on the repeat dose toxicity studies.

## 2.3.5. Ecotoxicity/environmental risk assessment

The available data do not allow to conclude definitively on the potential risk of Inclisiran to the environment. The applicant provided an environmental risk assessment (ERA) in accordance to the EMA guideline EMEA/CHMP/SWP/4470/00 (2006, corr 2). The ERA consists of a Phase I assessment. The calculated PEC value exceeds the action limit in Phase I, therefore, a Phase II assessment is required. The required Phase II assessment is pending, and its submission is committed by the applicant until 2021.

In reference to the provided log $D_{OW}$ no further PBT assessment is necessary.

## 2.3.6. Discussion on non-clinical aspects

The pharmacology, safety pharmacology, pharmacokinetics, and toxicology of inclisiran were evaluated in a series of in vitro and in vivo nonclinical studies. The nonclinical testing strategy for inclisiran was consistent with existing regulatory guidance and scientific advises obtained during the development process. All pivotal studies were conducted in accordance with the Good Laboratory Practice (GLP). In one 4 weeks rat study technical inaccuracies were detected during the assessment process. However, these shortcomings do not influence the overall conclusion on the data set submitted. Despite there were some deviations in the non-clinical development program, no major concerns have been identified from non-clinical point of view and the applicant was able to respond adequately on the various Other Concerns initially raised.

Pharmacodynamics of inclisiran was demonstrated in transgenic mice and monkeys.

The four animal species used for non-clinical studies, especially the general and reproductive toxicology studies, are considered relevant. Non-clinical pharmacokinetic studies demonstrated after SC administration preferred liver uptake, the site of intended action of inclisiran. In the rat SC injection sites were investigated and it was shown that the highest tissue concentration was demonstrated for this tissue. This phenomenon is not species specific.

The studies on toxicity identified no overt toxicity. Inclisiran showed no reproductive toxicity. The calculated safety margins are based on the highest dose applied and are based on the NOAEL doses in the pivotal chronic toxicity studies. They are 99-fold and 101-fold based on $C_{max}$ and 48.9-fold and 99.6-fold based on AUC in rats and monkeys, respectively, compared to the 300 mg human clinical dose. The safety margins obtained in reproductive toxicity studies are slightly lower, but sufficient. These safety margins are based on exposures generated from studies of once monthly dosing. The

applicant points out that these would cover considerably more frequent administrations than the recommended dosing regimen of 300 mg initially, again at 3 months, and then every 6 months.

The dose regime used in non-clinical toxicology studies induces a persistent reduction in the lipid profile, which equals the effects seen in humans with the intended clinical application scheme. Considering this aspect, the data supports the application of 11 injections, which would equal more than 4 years of clinical use. Considering this aspect, the high inclisiran concentrations remaining at the injection sites may be of importance. However, provided that various injection sites will be used in clinical practice no overt local effects are expected.

### 2.3.7. Conclusion on the non-clinical aspects

Inclisiran showed no overt toxicity in the repeated dose toxicity studies in rats and monkeys. Inclisiran showed no reproductive toxicity. Inclisiran was not genotoxic in vitro and in vivo nor revealed it a carcinogenic potential in rats and mice. There are no objections against marketing authorisation from the nonclinical viewpoint.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The human pharmacokinetics (PK) and pharmacodynamics (PD) of inclisiran were evaluated in a comprehensive clinical pharmacology programme which included 3 phase I, 4 phase II, and 6 phase III studies (3 of which are still ongoing) in support of the safe and effective use of inclisiran in patients with hyperlipidaemia.

**Table 3.3.1: Inclisiran Clinical Pharmacology Programme**

| Study | Objective | Study Design | Population | Test Products | Number of Subjects |
|---|---|---|---|---|---|
| ALN-PCSSC-001<br>Phase I | To evaluate the safety and tolerability of inclisiran when administered SC as a single dose or multiple doses to subjects with elevated LDL-C. | Randomised, single-blind, placebo-controlled, SAD and MD study | Healthy subjects with elevated serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) at screening | SAD Phase<br>25 mg or placebo<br>100 mg or placebo<br>300 mg or placebo<br>500 mg or placebo<br>800 mg or placebo | SAD Phase<br>24 subjects<br>19 M / 5 F<br>MD Phase<br>45 subjects<br>29 M / 16 F |

| | | | | | |
|---|---|---|---|---|---|
| | | | | MD Phase (Off statin co-medication)<br>300 mg monthly x2 or placebo<br>500 mg monthly x2 or placebo<br>125 mg QWx4 or placebo<br>250 mg Q2Wx2 or placebo;<br>MD Phase (On statin co-medication)<br>300 mg monthly x2 or placebo<br>500 mg monthly x2 or placebo | |
| ORION-1<br>(MDCO-PCS-15-01)<br>Phase II | To evaluate the effect of inclisiran treatment on LDL-C levels at Day 180. | Placebo-controlled, double-blind, randomised trial | Subjects with ASCVD or ASCVD-risk equivalents and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapy | Single dose (Day 1 only)<br>200 mg or placebo x 1<br>300 mg or placebo x 1<br>500 mg or placebo x 1 (500 mg<br>dose given as two injections)<br>Two doses (Day 1 and Day 90)<br>100 mg or placebo x 2<br>200 mg or placebo x 2<br>300 mg or placebo x 2 | 501<br>326 M / 175 F |
| ORION-2<br>(MDCO-PCS-16-02)<br>Phase II | To characterise the effect of 90 and 180 days of SC inclisiran on the % change from Day 1 in LDL-C in subjects with HoFH. | Open label, single arm, multicentre pilot study | Subjects with HoFH | 300 mg inclisiran SC | 4<br>2 M / 2 F |
| ORION-3<br>(MDCO-PCS-16-01)<br>Phase II | To evaluate the effect of inclisiran treatment on LDL-C levels at Day 210 compared to Baseline of ORION-1 in Group 1 (inclisiran only arm). | Open label, long term extension study with an active comparator (evolocumab) | Subjects with ASCVD or ASCVD-risk equivalents and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapy | Group 1 (Inclisiran Only Arm):<br>300 mg inclisiran s.c<br>Group 2 (Switching Arm):<br>Evolocumab 140 mg | 374<br>(treated)<br>ongoing |

| | | | | | |
|---|---|---|---|---|---|
| ORION-4<br>(MDCO-PCS-17-01)<br>Phase III | Intention-to-treat comparison among all randomised participants of the effects of allocation to inclisiran versus placebo on time to first occurrence of major adverse cardiovascular events (MACE) | Double-blind randomised placebo-controlled trial | Subjects with ASCVD | 300 mg inclisiran SC or placebo | 15,000<br>ongoing |
| ORION-5<br>(MDCO-PCS-17-02)<br>Phase III | To evaluate the effect of inclisiran treatment on LDL-C levels at Day 150. | Phase III, two-part (double-blind placebo-controlled/ open-label) multicentre study | Subjects with HoFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies | 300 mg inclisiran SC or placebo | 56<br>ongoing |
| ORION-6<br>(MDCO-PCS-18-02)<br>Phase I | To quantify the effect of different degrees of hepatic impairment CP A and B compared to normal subjects on the PK and the PD of inclisiran in order to develop dosing recommendations for subjects with hepatic impairment. | Single-dose, open-label, parallel-group study | Subjects with normal renal function and subjects with mild, moderate and severe renal impairment | 300 mg inclisiran SC | 28<br>16 M / 12 F |
| ORION-7<br>(MDCO-PCS-16-03)<br>Phase I | To quantify the effect of different degrees of renal impairment on the PK of inclisiran, and to assess safety and tolerability in order to develop dosing recommendations for subjects with renal impairment. | Single-dose, open-label, parallel-group study | Subjects with normal renal function and subjects with mild, moderate and severe renal impairment | 300 mg inclisiran SC | 31<br>22 M / 9 F |
| ORION-8<br>(MDCO-PCS-17-05)<br>Phase III | To evaluate the effect of inclisiran treatment on the proportion of subjects achieving prespecified LDL-C targets at end of study and the safety and tolerability | Long term extension trial of the Phase III lipid lowering trials | Subjects with ASCVD, ASCVD-risk equivalents (e.g., diabetes and FH), HeFH, or HoFH, and elevated LDL-C despite maximum tolerated dose of LDL-C lowering | 300 mg inclisiran SC or placebo | 3700<br>ongoing |

| | | | | | |
|---|---|---|---|---|---|
| | profile of long term use of inclisiran. | | therapies who have completed one of the phase III lipid-lowering feeder studies (ORION-9, ORION-10, ORION-11 or ORION-5) | | |
| ORION-9<br>(MDCO-PCS-17-03)<br>Phase III | To evaluate the effect of inclisiran treatment on: LDL-C levels at Day 510 and time adjusted percent change in LDL-C levels from baseline between Day 90 and Day 540 levels. | Placebo-controlled, double-blind, randomised trial | Subjects with HeFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies | 300 mg inclisiran SC or placebo | 482<br>227 M / 255 F |
| ORION-10<br>(MDCO-PCS-17-04)<br>Phase III | To evaluate the effect of inclisiran treatment on: LDL-C levels at Day 510 and time adjusted percent change in LDL-C levels from baseline between Day 90 and Day 540 levels. | Placebo-controlled, double-blind, randomised trial | Subjects with atherosclerotic cardiovascular disease (ASCVD) and elevated low-density lipoprotein cholesterol (LDL-C) despite maximum tolerated dose of LDL-C lowering therapies | 300 mg inclisiran SC or placebo | 1561<br>1083 M / 478 F |
| ORION-11<br>(MDCO-PCS-17-08)<br>Phase III | To evaluate the effect of inclisiran treatment on: LDL-C levels at Day 510 and time adjusted percent change in LDL-C levels from baseline between Day 90 and Day 540 levels. | Placebo-controlled, double-blind, randomised trial | Subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C) | 300 mg inclisiran SC or placebo | 1617<br>1160 M / 457 F |
| ORION-12<br>(MDCO-PCS-17-09)<br>Phase I | To assess the effect of a supratherapeutic dose of inclisiran on cardiac repolarisation as assessed by the QTc interval corrected forHR using the QTcF. | Randomised, double-blind, double-dummy, placebo- and positive controlled, crossover study | Healthy subjects | 300 mg inclisiran SC or placebo<br>400 mg oral moxifloxacin | 48<br>33 M / 15 F |

## 2.4.2. Pharmacokinetics

Inclisiran is a double-stranded 21-23mer small interfering ribonucleic acid (siRNA) designed to inhibit the production of proprotein convertase subtilisin/kexin type 9 (PCSK9). Inclisiran is conjugated at the sense strand with triantennary GalNAc to facilitate hepatic uptake via the asialoglycoprotein receptor (ASGPR).
Inclisiran is intended for use as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidaemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C). It is administered by subcutaneous (SC) injection from a prefilled syringe at a dose of 300 mg inclisiran sodium (284 mg inclisiran free acid).

No absolute bioavailability and absorption, distribution, metabolism, and excretion (ADME) studies in human have been performed for inclisiran. The PK of inclisiran in human has been evaluated in four Phase I studies (ALN-PCSSC-001, ORION-6, ORION-7 and ORION-12) following single subcutaneous doses of 25 mg to 900 mg inclisiran sodium.
No relative bioavailability or bioequivalence studies have been conducted, since the drug product used throughout the clinical program was the same except for the volume filled in the single-use container and a change from single-use vial to the prefilled syringe with no concomitant changes in PD effects, safety or tolerability of inclisiran noted.

Plasma concentrations are not directly related to the pharmacodynamic effects, which last for several months. Due to the large temporal disconnect observed, the dose-response relationship was characterised using a population PD model.

### *Absorption*

After a 300mg single dose inclisiran sodium SC in healthy human subjects, inclisiran is absorbed from the SC injection site (abdomen) into plasma with median $T_{max}$ (range) of 6 hours (0.5 to 12 hours) and is detectable in plasma up to 48 hours post dose. Inclisiran is rapidly cleared from the plasma with a mean half-life (t½) of 9.58 hours and mean $C_{max}$ and $AUC_{0\text{-}inf}$ amounted to 509 ng/mL and 7980 ng/mL*h, respectively.

PK of inclisiran after single SC administration of 300mg inclisiran sodium appeared similar in subjects with elevated LDL-C as compared to healthy subjects.
After multiple dose SC administration of 300mg inclisiran sodium, means for $C_{max}$, $AUC_{0\text{-}tau}$ and t½ in subjects with elevated LDL-C were 750 ng/mL, 15586 ng/mL*h and 3.59 h off statins, and 1252 ng/mL, 18860 ng/mL*h and 7.36 h on statins, respectively.

### *Distribution*

The apparent volume of distribution of inclisiran was estimated approximately 500 L in healthy adults following single 300 mg SC doses of inclisiran sodium. Apparent clearance in healthy subjects was estimated 38.1 L/hour.

### *Elimination*

Apparent clearance in healthy subjects was estimated 38.1 L/hour.
Based on non-clinical data, initial blood clearance of inclisiran appears to occur through high liver distribution. It was estimated that approximately 82.5% elimination of inclisiran from plasma is due to hepatic uptake. Besides hepatic uptake, renal clearance was identified a main route of elimination of

unchanged inclisiran from plasma in human. 15.9% of unchanged inclisiran was excreted in urine over 48 hours following a single oral SC dose of 300 mg inclisiran sodium. The mean (SD) renal clearance (CLR) was 6.18 (1.62) L/h in healthy subjects.
Although rapidly cleared from plasma, inclisiran exhibits a slow elimination half-life from liver based on non-clinical QWBA (270 hours in rats; > 1980 hours in monkeys), and does not appear to undergo extensive metabolism.
The metabolism of inclisiran was evaluated *in vitro* in human, mouse, rat and monkey serum and liver S9 fractions, and *in vivo* in rat and monkey plasma and liver samples. While inclisiran was relatively stable after 24 hours incubation in human serum *in vitro* with 80% of the antisense and 87% of the sense strand remaining, in human liver S9 fractions, slow degradation especially of the antisense strand appears to take place with only 41% of the antisense and 71% of the sense strand remaining after 24 hours incubation. Metabolic profiling in human serum and liver S9 fractions did not identify any metabolites unique to human *in vitro.* Inclisiran appears to be primarily metabolised by non-specific nucleases to shorter nucleotides of varying length.
*In vivo*, full-length inclisiran parent was the major component in human plasma obtained from healthy subjects. The AS(n-1)3' and AS(n-1)5' metabolites were also detected and their kinetics appeared to parallel that of inclisiran. The plasma concentration ratios of metabolite AS(n-1) relative to the parent AS strand increased from 0.5 hours to 48 hours post dose. Metabolites AS(n-2)3' and AS(n-2)5' were not detected. Metabolic profiling has not been investigated in clinical urine samples.

As in the renal impairment study ORION-7, unexplained high antisense to sense strand ratios above the normal range were observed for inclisiran in several subjects with renal impairment, especially in urine, but not in subjects with normal renal function in this and other studies, and also not in the urine of monkeys in non-clinical studies, and the safety data in severe renal impairment are too limited to draw a definite conclusion, inclisiran should be used with caution in patients with severe renal impairment which is reflected in the PI.

The applicant argued that the potential of the antisense strand or metabolites thereof for off-target effects is negligible. From a set of 20 potential off-target transcripts identified by an in silico approach, the response of 18 transcripts endogenously expressed in the hepatocyte cell line Hep3b was measured by quantitative PCR (qPCR) and no substantial inhibition by inclisiran was found. However, two potential targets, namely SULF1 (NM_015170.2) and FAM196B (NM_001129891.1), could not be analysed in this study because they are not expressed in the hepatocyte cell line Hep3b. The applicant stated that as inclisiran is targeted to the liver and has not been shown to silence genes in tissues outside of liver, these two targets were not considered as genes that could be silenced by inclisiran. The applicant did not provide any information on whether these two transcripts are expressed in the renal tubular epithelial cells, or in other cells for which there is evidence of ASGPR expression, such as dendritic cells and monocytes. Hence, the possibility for off-target effects of inclisiran cannot be fully ruled out.

## *Dose proportionality and time dependencies*

Inclisiran PK was found approximately dose proportional in subjects with elevated LDL-C, with doses ranging from 25 mg to 800 mg, and does not accumulate with multiple dosing.
The variability appeared mostly moderate, although high variability was sometimes observed.

*In vitro* plasma protein binding was concentration dependent with higher protein binding at lower inclisiran concentrations. At therapeutic concentrations, inclisiran was approximately 87% protein bound in human plasma.

## *Special populations*

Evaluation of the effects of body weight, age, gender and race on inclisiran PK suggested that only body weight was a statistically significant covariate on inclisiran PK parameters ($p < 0.001$), $T_{max}$ excluded. Age (in the analysed range of 20 to 70 years), gender and race had no impact on inclisiran PK. The observed differences in PK of inclisiran by body weight do not appear to have any significant impact on the overall clinical response to inclisiran treatment based on the population PD analyses.

The effect of mild, moderate and severe renal impairment on the PK of inclisiran has been investigated in a dedicated study (ORION-7). Significant increases in inclisiran exposures were revealed, with greatest increases (3.31-fold for $C_{max}$ and 2.33-fold for $AUC_{0-48}$) in subjects with severe renal impairment. However, inclisiran was not detectable in the plasma of any of the patient groups beyond 48 hours and higher exposure of inclisiran was not correlative to the PD response.
The effect of end-stage renal disease (ESRD) and of haemodialysis on inclisiran PK have not been studied. Based on the relationship observed between inclisiran clearance (systemic and renal) and creatinine clearance, an increase in inclisiran exposures to levels that are not higher than the exposures observed in prior clinical studies and considered safe was predicted. It was concluded that no dose adjustment of inclisiran in subjects with mild, moderate, severe renal impairment, as well as ESRD is necessary. Given the infrequent and transient exposures to inclisiran that can be expected based on the long dosing interval (initially, after 3 months and then every 6 months) and short t½ of inclisiran in plasma, this appeared acceptable. However, based on differences in the antisense to sense ratios noted solely in several subjects with renal impairment (see above) and the safety data in severe renal impairment being too limited to draw a final conclusion, inclisiran should be used with caution in patients with severe renal impairment. As regards the effect of haemodialysis, the applicant reasoned that as inclisiran was undetectable in the plasma of patients with severe renal impairment within 72 hours or less, it is recommended to dose inclisiran at least 72 hours before or any time after a haemodialysis session to avoid any potential impact on inclisiran PK.

The effect of mild (Child Pugh A) and moderate (Child Pugh Class B) hepatic impairment on PK of inclisiran has been evaluated in a dedicated study (ORION-6). Inclisiran exposure increased with hepatic impairment. While subjects with mild hepatic impairment had similar inclisiran $C_{max}$ and 1.33-fold higher inclisiran $AUC_{inf}$, subjects with moderate hepatic impairment had 2.1-fold higher inclisiran $C_{max}$ and 2.04-fold higher inclisiran $AUC_{inf}$ as compared to subjects with normal hepatic function, respectively. Regardless of hepatic status, inclisiran was undetectable in plasma within 96 hours.
It was concluded that no dose adjustment of inclisiran is considered necessary in subjects with mild or moderate hepatic impairment. The ORION-6 study did not include subjects with severe hepatic impairment, therefore the effects of inclisiran in these subjects are unknown. Based on the linear regression analyses, subjects with severe hepatic impairment are anticipated to have $C_{max}$ and AUC that are approximately 2.5- to 4-fold higher than the respective mean exposures in subjects with normal hepatic function, which is still less than the exposures observed in prior clinical studies and considered safe. It is proposed that inclisiran should be used with caution in patients with severe hepatic impairment as no data are available.
Overall, hepatic impairment increases systemic exposure in the plasma but the half-life of inclisiran remains short and levels are undetectable within 96 hours as compared to 48h in normal hepatic function. According to the applicant, there is currently no evidence from non-clinical and clinical studies to suggest that this temporary and modest increase in systemic exposure correlates to an impact on the safety profile of inclisiran.

## *Pharmacokinetic interaction studies*

The results of *in vitro* DDI assessments indicated a very low risk for CYP- or transporter-related clinical PK interactions at clinically relevant concentrations; therefore, no dedicated *in vivo* DDI studies were performed. *In vitro*, inclisiran showed no direct inhibitory potential against CYP1A2, CYP2B6, CYP2C8. CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 with $IC_{50}$ values of >612 µM in all cases. Inclisiran had no potential for time-dependent inhibition of these CYP enzymes at concentrations up to 612µM. Inclisiran showed no potential for induction of CYP3A4, CYP2B6 and CYP1A2. It is anticipated that inclisiran is not a substrate for CYP enzymes, but this has not been investigated and is reflected accordingly in the PI. Inclisiran is not an inhibitor of human OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, MATE2k, MDR1, or BCRP *in vitro*. No active inclisiran transport was observed for human OAT3, OCT2, OATP1B1, OATP1B3, MATE1, MATE2k, MDR1, or BCRP *in vitro*. Active OAT1 transport could not be completely excluded, but is not likely. Inclisiran is not a substrate or an inhibitor of human OCT1, OCT3 or BSEP transporters *in vitro*.

The potential risk of PK DDI upon statin coadministration was investigated in ALN-PCSSC-001 (effect of statin on inclisiran PK) and ORION-10 (effect of inclisiran on statin PK). In study ALN-PCSSC-001, co-administration resulted in slightly increased plasma exposure to inclisiran, and at the 300 mg dose level in higher t½, lower CL/F, CLR and Fe values, but the effect appeared to be attenuated at higher dose level, especially after multiple dose administration. In study ORION-10, PK drug-drug interaction between inclisiran as a perpetrator and atorvastatin or rosuvastatin could not be ruled out. However, based on limitations observed (i.a. noncrossover study design, the very small number of subjects (ALN-PCSSC-001), and very sparse PK sampling, variability observed and population PK model applied (ORION-10)), the conclusions to be drawn from the two studies are limited. Based on the totality of the data, including assumed lack of biological plausibility of a PK interaction, the long dosing interval and short t1/2 of inclisiran, it was concluded that there is no clinically significant drug-drug interaction between statins and inclisiran and that statins and inclisiran can be co-administered in combination without a need for statin dose adjustment.

## *Overall conclusion on PK*

No absolute bioavailability and human absorption, distribution, metabolism, and excretion (ADME) studies have been performed for inclisiran. Given these limitations, and the lack of metabolic profiling in clinical urine samples, pharmacokinetics of inclisiran has been sufficiently characterised. Inclisiran is absorbed from the SC injection site (abdomen) into plasma with $T_{max}$ ranging between 0.5 to 12 hours and is detectable in plasma up to 48 hours post dose. Inclisiran is rapidly cleared from the plasma with a half-life of ~9 hours. Based on non-clinical studies, the majority of inclisiran is taken up by the liver, the target organ of effect. Renal clearance is a main route of elimination of unchanged inclisiran from plasma in human; about 16% of unchanged inclisiran is excreted in urine following single SC administration of 300 mg inclisiran sodium. Inclisiran PK is approximately dose proportional with doses ranging from 25 mg to 800 mg, has a short plasma half-life, and does not accumulate with multiple dosing. Based on *in vitro* data, there is a low risk for CYP- or transporter-related clinical PK interactions at clinically relevant concentrations. Plasma concentrations are not directly related to the pharmacodynamic effects, which last for several months. The applicant has not proposed any changes to the dosing recommendations in subjects with various stages of renal impairment as well as in subjects with mild and moderate hepatic impairment despite significant increases in exposures observed in these subjects as compared to healthy subjects. This may be acceptable from a PK point of view, given the infrequent and transient exposures to inclisiran that can be expected based on the long dosing interval (initially, after 3 months and then every 6 months) and short t½ of inclisiran in plasma, however as differences in the antisense to sense ratios have been noted solely in several subjects with

renal impairment and the safety data in severe renal impairment is too limited to draw a final conclusion, inclisiran should be used with caution in patients with severe renal impairment. Plasma concentrations are not directly related to the pharmacodynamic effects, which last for several months.

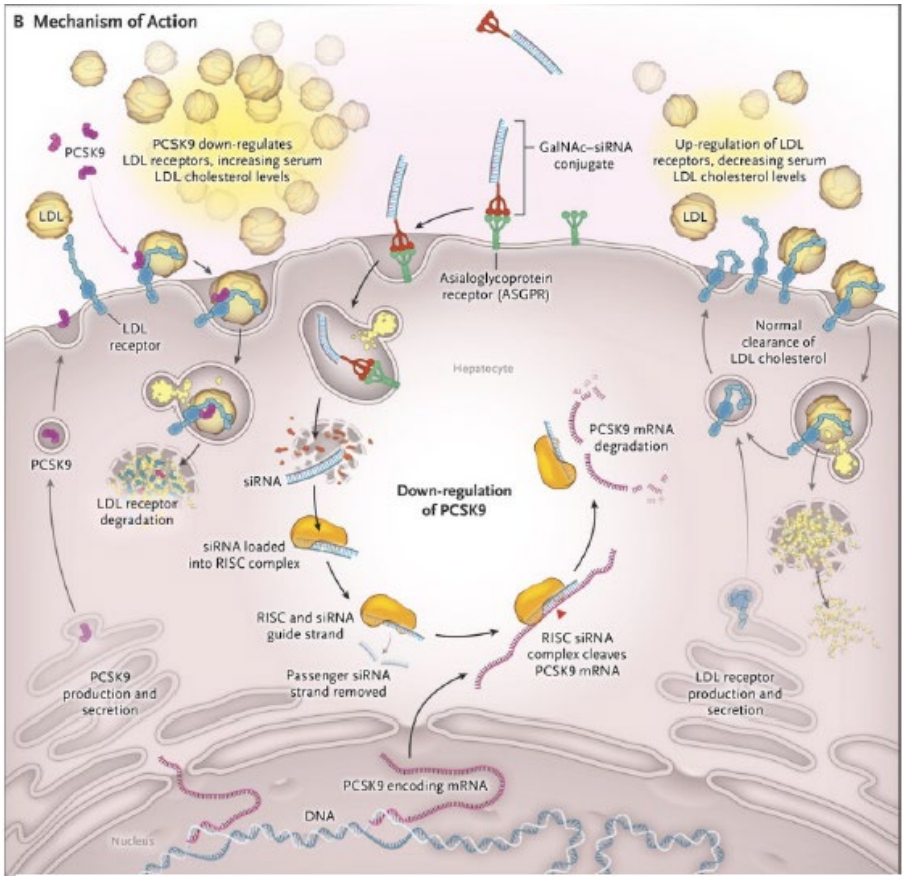
## 2.4.3. Pharmacodynamics

### *Mechanism of action*

Inclisiran is a chemically synthesised, long-acting, subcutaneously delivered, siRNA double-stranded oligonucleotide directed against PCSK9 that is covalently linked to a ligand containing three GalNAc residues. These carbohydrates bind to abundant liver-expressed asialoglycoprotein receptor (ASGPR), leading to inclisiran uptake specifically into hepatocytes.

When introduced into the hepatocyte, inclisiran engages the natural pathway of RNA interference (RNAi) by binding intracellularly to the RISC, enabling it to cleave messenger RNA (mRNA) molecules encoding PCSK9 specifically. The cleaved PCSK9 mRNA is degraded and thus unavailable for protein translation, which results in decreased levels of the PCSK9 protein. A single siRNA-bound RISC is catalytic and cleaves many transcripts and the duration of action is anticipated to be longer than other mechanisms.

**Figure 3.3.2.1: Mechanism of Action of Inclisiran**




Source: N Engl J Med. Khorova A. Oligonucleotide Therapeutics — A New Class of Cholesterol-Lowering Drugs. 376;1:4-7. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

The decrease in PCSK9 triggers a reduced breakdown of LDLR and thus an increased reduction of LDL-C in plasma.

## *Primary and Secondary pharmacology*

Phase I and phase II PK / PD studies

The proof-of concept first in human study in healthy subjects, a PD single- and multiple-ascending dose study (ALN-PCSSC-001), showed that the dose response for decrease in PCSK9 over time correlated well with the dose responses for a decrease in LDL-C.

The study was designed to evaluate the safety, tolerability, PK, and PD of ALN-PCSSC in 2 phases: a single ascending dose (SAD) phase and a multiple dose (MD) phase. The enrolled cohorts are presented in the table below.

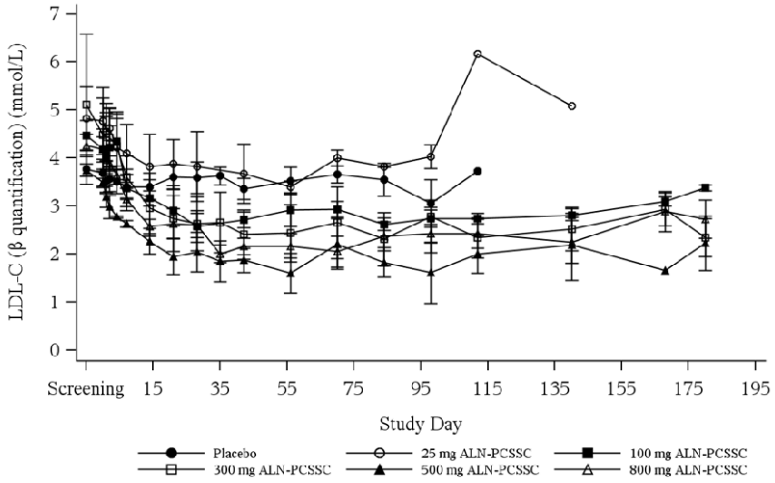
**Table 3.3.2.1: Planned and Optional Cohorts Enrolled in Study ALN-PCSSC-001**

| Phase<br>Number of Planned Subjects<br>(ALN-PCSSC:Placebo) | | Cohort | Planned or Optional |
|---|---|---|---|
| SAD Phase<br>4 (3:1) | | 25 mg ALN-PCSSC or placebo | Planned |
| | | 100 mg ALN-PCSSC or placebo | Planned |
| | | 300 mg ALN-PCSSC or placebo | Planned |
| | | 500 mg ALN-PCSSC or placebo | Planned |
| | | 800 mg ALN-PCSSC or placebo | Planned |
| | | 800 mg ALN-PCSSC or placebo | Optional |
| MD Phase<br>8 (3:1 in blocks of 4) | Off statin co-medication | 300 mg Monthly x2 ALN-PCSSC or placebo | Planned |
| | | 500 mg Monthly x2 ALN-PCSSC or placebo | Planned |
| | | 125 mg QWx4 ALN-PCSSC or placebo | Optional |
| | | 250 mg Q2Wx2 ALN-PCSSC or placebo | Optional |
| | On statin co-medication | 300 mg Monthly x2 ALN-PCSSC or placebo | Planned |
| | | 500 mg Monthly x2 ALN-PCSSC or placebo | Planned |

In the SAD phase, subjects with LDL-C ≥2.6 mmol/L (≥100 mg/dL) who were not on statin medication were enrolled in a total of 6 cohorts. Each cohort was composed of 4 subjects randomised 3:1 to receive a single dose of ALN-PCSSC or placebo, respectively.

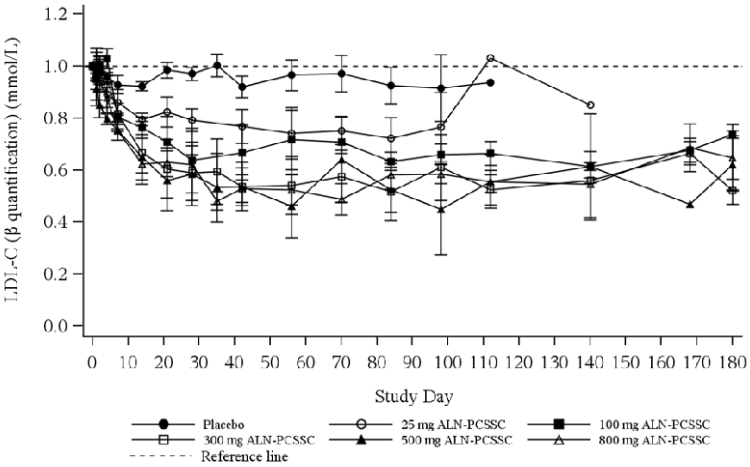
The mean (SD) baseline LDL-C concentrations ranged from 3.50 (0.149) mmol/L to 4.76 (1.210) mmol/L across treatment groups. A dose-dependent reduction in LDL-C concentrations was observed up to 300 mg inclisiran as single dose, at which there was a plateauing of dose effect, and was maintained through Day 180, the last day measured, in all inclisiran treatment groups, except for the 25 mg dose.

**Figure 3.3.2.2: Arithmetic Mean (SE) of Absolute LDL-C in the SAD Phase – Pharmacodynamic Population**




Abbreviations: LDL-C=low-density lipoprotein cholesterol; SAD=single ascending dose; SE=standard error.
Source: Figure 14.2-1.1.1.

**Figure 3.3.2.3: Arithmetic Mean (SE) of LDL-C Relative Change in the SAD Phase – Pharmacodynamic Population**

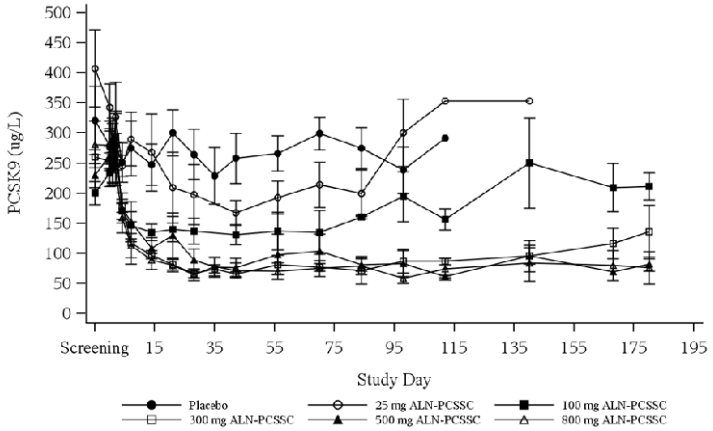



Abbreviations: LDL-C=low-density lipoprotein cholesterol; SAD=single ascending dose; SE=standard error.
Note: Day 0 reflects the baseline value.
Note: Figure displays change relative to baseline; units in the y-axis label correspond to the laboratory value prior to division by baseline.
Source: Figure 14.2-1.2.1.

The largest mean percent reduction from baseline at the individual nadir was observed at 800 mg inclisiran (-59.2%) and at the group nadir at 500 mg inclisiran (-55.1% at Day 98).

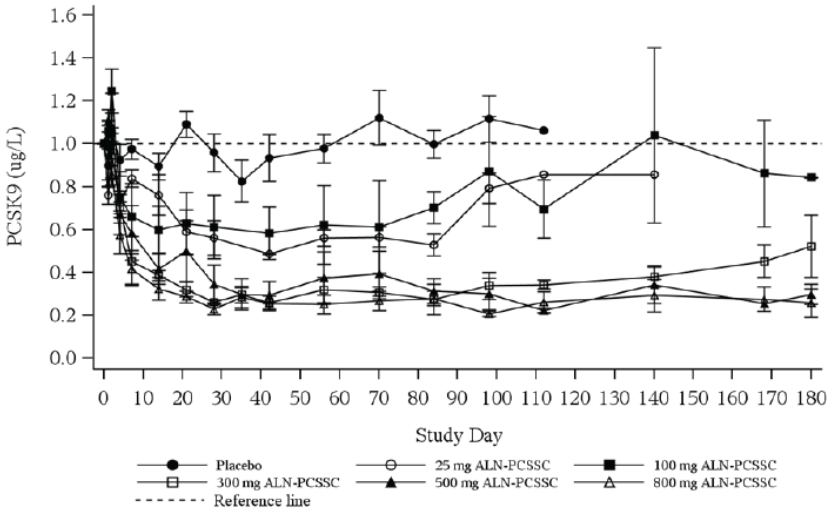
The mean (SD) baseline PCSK9 concentrations ranged from 233.77 (39.167) µg/L to 342.65 (67.893) µg/L across treatment groups. A dose-dependent reduction in PCSK9 concentrations was observed up to 300 mg inclisiran, at which there was a plateauing of dose effect. Reductions in PCSK9 from baseline were maintained through Day 180, the last day measured, in all inclisiran treatment groups, except for the 25 mg and 100 mg doses.

**Figure 3.3.2.4: Arithmetic Mean (SE) of Absolute PCSK9 in the SAD Phase – Pharmacodynamic Population**




Abbreviations: PCSK9=proprotein convertase subtilisin/kexin type 9; SAD=single ascending dose; SE=standard error.
Source: Figure 14.2-1.1.1.

**Figure 3.3.2.5: Arithmetic Mean (SE) of PCSK9 Relative Change in the SAD Phase – Pharmacodynamic Population**

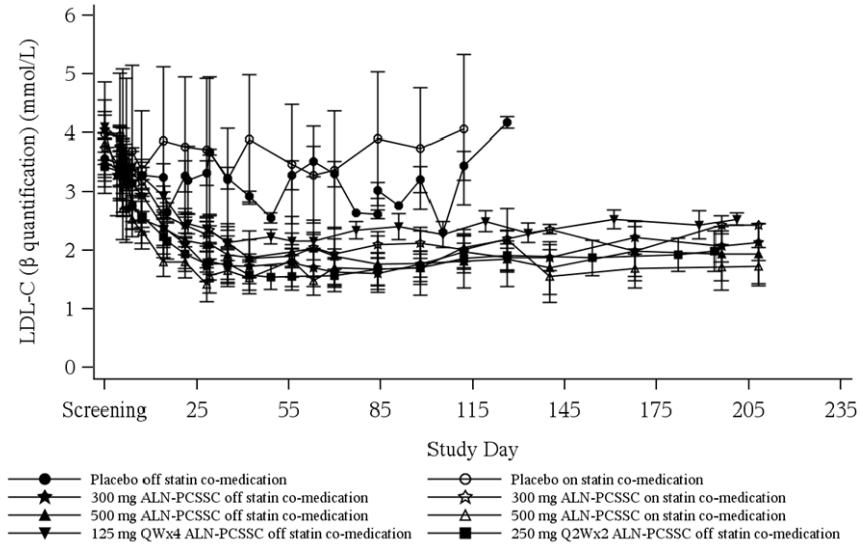



The largest mean percent reduction from baseline at the individual nadir was observed at 800 mg inclisiran (-82.3%) and at the group nadir at 800 mg inclisiran (79.4% at Day 98).

In the MD phase, subjects with LDL-C ≥2.6 mmol/L (≥100 mg/dL) were enrolled in 6 cohorts (4 cohorts of subjects without statin co-medication, 2 cohorts of subjects with statin co-medication). Each cohort was composed of 8 subjects randomised 3:1 (in blocks of 4 subjects) to ALN-PCSSC or placebo, respectively.

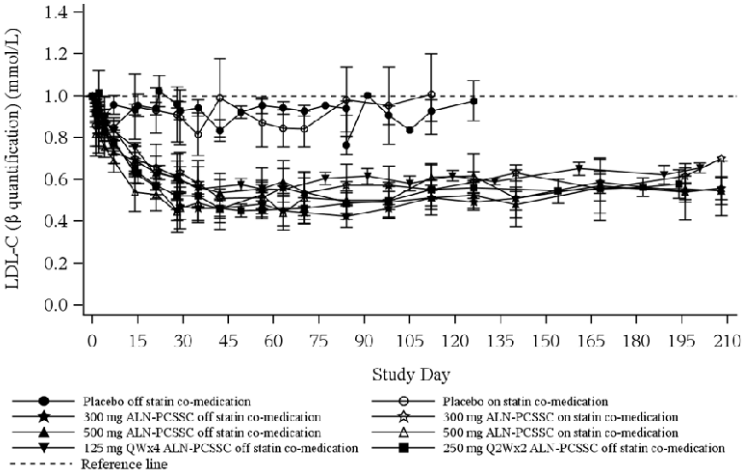
The mean (SD) baseline LDL-C concentrations ranged from 3.35 (0.643) mmol/L to 3.93 (1.864) mmol/L across treatment groups. A plateauing of dose effect was observed for all inclisiran dose groups and dose frequencies. Reductions in LDL-C from baseline were maintained through 180 days after the last dose for each inclisiran treatment group.

**Figure 3.3.2.6: Arithmetic Mean (SE) of Absolute LDL-C in the MD Phase – Pharmacodynamic Population**




Abbreviations: MD=multiple dose; LDL-C=low-density lipoprotein cholesterol; SE=standard error.
Source: Figure 14.2-1.1.2.

**Figure 3.3.2.7: Arithmetic Mean (SE) of LDL-C Relative Change in the MD Phase – Pharmacodynamic Population**

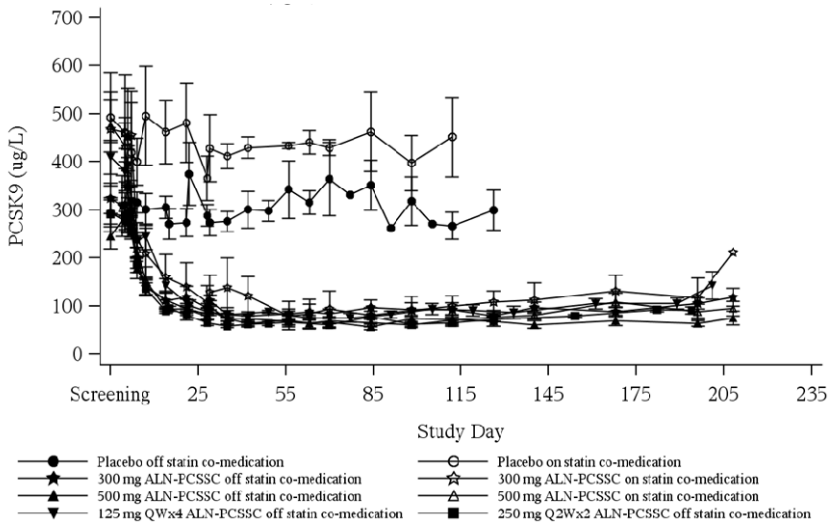



Abbreviations: MD=multiple dose; LDL-C=low-density lipoprotein cholesterol; SE=standard error.
Note: Day 0 reflects the baseline value.
Note: Figure displays change relative to baseline; units in the y-axis label correspond to the laboratory value prior to division by baseline.
Source: Figure 14.2-1.2.2.

The largest mean percent reduction of LDL-C from baseline at the individual nadir was observed at 300 mg inclisiran without statin (-64.4%) and at the group nadir at 300 mg inclisiran without statin (55.7% at Day 70). The mean percent reductions at the individual and group nadirs were similar within 300 mg and 500 mg groups regardless of statin co-medication use and the time to group nadir was the same at each dose level.

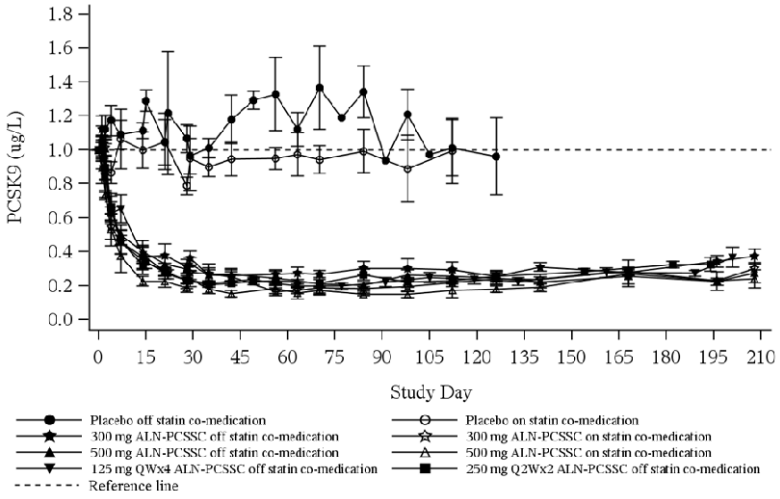
The mean (SD) baseline PCSK9 concentrations ranged from 276.23 (58.686) µg/L to 460.69 (209.435) µg/L across treatment groups, including subjects who received placebo. A plateauing of dose effect was observed for all inclisiran dose groups and dose frequencies. Reductions in PCSK9 from baseline were maintained through 180 days after the last dose for each inclisiran treatment group.

**Figure 3.3.2.8: Arithmetic Mean (SE) of Absolute PCSK9 in the MD Phase – Pharmacodynamic Population**




Abbreviations: MD=multiple dose; PCSK9=proprotein convertase subtilisin/kexin type 9; SE=standard error.
Source: Figure 14.2-1.1.2.

**Figure 3.3.2.9: Arithmetic Mean (SE) of PCSK9 Relative Change in the MD Phase – Pharmacodynamic Population**




Abbreviations: MD=multiple dose; PCSK9=proprotein convertase subtilisin/kexin type 9; SE=standard error.
Note: Day 0 reflects the baseline value.
Note: Figure displays change relative to baseline; units in the y-axis label correspond to the laboratory value prior to division by baseline.
Source: Figure 14.2-1.2.2.

The largest mean percent reduction from baseline at the individual nadir was observed at 500 mg inclisiran with statin (-88.5%) and at the group nadir at 500 mg inclisiran with statin (85.2% at Day 84). The mean percent reductions at the individual nadirs were similar within 300 mg and 500 mg groups regardless of statin co-medication use, and the time to group nadir was the same at each dose level.

In both administration phases dose-dependent reductions from baseline were observed in total cholesterol (TC), non-HDL-C, and apo-lipoprotein B (Apo-B), with a plateauing of dose effect observed at 300 mg inclisiran.

Reductions were also observed in lipoprotein(a) [Lp(a)] beginning at 100 mg inclisiran. There were no dose-dependent trends in increases in HDL-C and apolipoprotein A1 (Apo-A1), with maximum increases observed at 300 mg inclisiran.

Exposure-response relationship phase II study

In the phase II study ORION-1, a randomised, double-blind placebo-controlled dose response study to assess the effect of inclisiran injection(s) on efficacy, safety, and tolerability in subjects with ASCVD or ASCVD-risk equivalents (e.g. diabetes and FH) and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies, the PK/PD relationship of 200 mg, 300 mg, and 500 mg inclisiran, respectively, administered as single dose or 100 mg, 200 mg, and 300 mg inclisiran on day 1 and day 90 as multiple dose has been investigated.

The primary efficacy endpoint was the percentage change in LDL-C from baseline to Day 180.

Secondary efficacy parameters included the change from baseline LDL-C, change from baseline in lipids and lipoproteins including TC, triglycerides, LDL-C, HDL-C, non-HDL-C, VLDL, Apo-A1, Apo-B, Lp(a), CRP, and PCSK9.

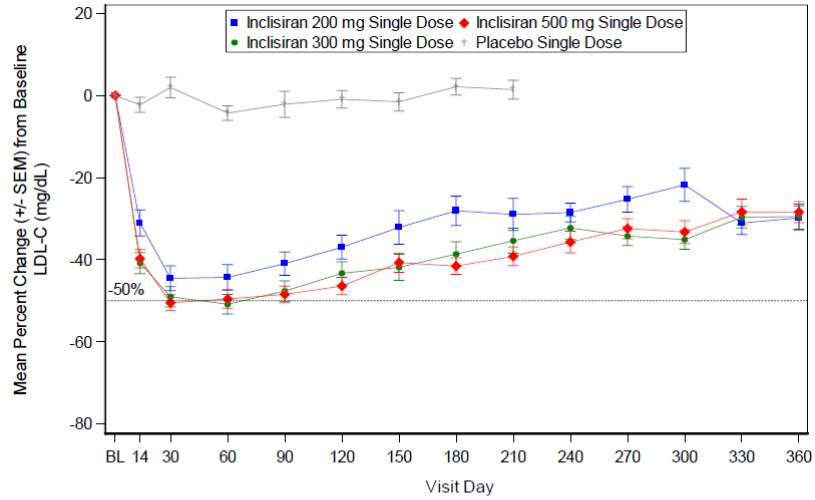
All randomised subjects who received at least one dose of study drug and had both the baseline and the 180-day follow-up LDL-C assessment. Treatment classification was based on the randomised treatment. This was the primary population for analysis of the primary and secondary endpoints (mITT-Population).

*Single dose group*

Results of study ORION-1 in the single dose groups for the primary endpoint showed a mean percentage LDL-C reduction of 27.9%, 38.4%, and 41.9% following single doses of 200 mg, 300 mg, and 500 mg inclisiran, respectively, compared to a 2.1% increase in the placebo group (all $p<0.0001$) for the mITT Population.

Results of the secondary endpoints percentage change in LDL-C from baseline to Days 14, 30, 60, 90, 104, 120, 150, 210, 240, 270, 300, 330, and 360 showed a LDL-C reduction at all timepoints with all doses of inclisiran. The LS mean reductions from baseline at specific timepoints (Days 30, 60, 90, 120, 150, and 180) ranged from 27.93% to 44.33% after a single dose of 200 mg, from 38.39% to 50.62% after a single dose of 300 mg, and from 41.10% to 50.87% after a single dose of 500 mg. In the placebo group, LS mean changes from baseline ranged between increases of 2.13% and decreases of 3.73% over time and the mean percent reduction from baseline at Day 360 was 29.8% after a single dose of 200 mg, 29.5% after a single dose of 300 mg, and 28.4% after a single dose of 500 mg. In the placebo group, the mean percent reduction from baseline at Day 360 was 13.4%.

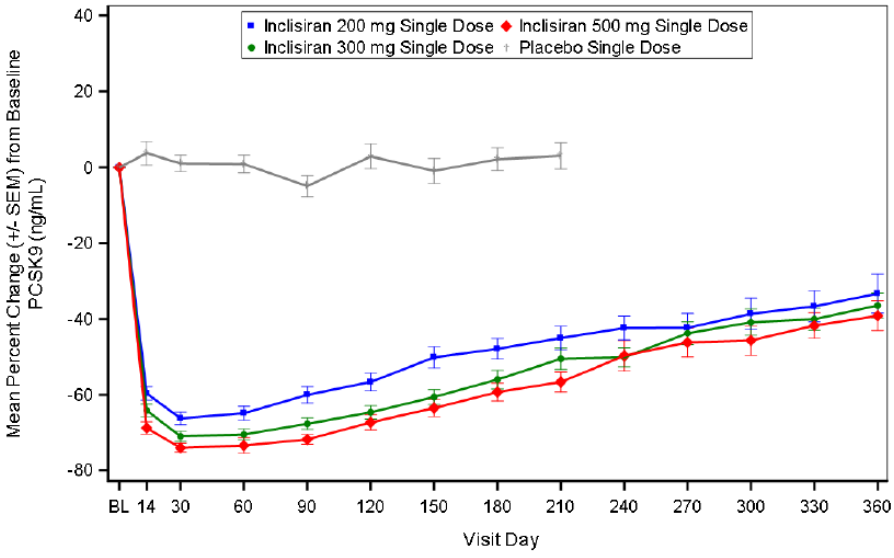
**Figure 3.3.2.10: Percent Change from Baseline Beta-Quantification LDL-C (mg/dL) by Dose Group over Time – mITT Population + Single Dose**




Source: Section 14.4, Figure 5.3.2.1
Note: Data for placebo-treated subjects are not presented beyond Day 210 since the majority of placebo-treated subjects did not have data collected beyond this timepoint. Data for the few placebo-treated subjects with beta-quantification LDL-C values collected beyond Day 210 maybe be found in Section 14.2.2.1, Table 5.4.2.1 which includes the beta-quantification LDL-C values along with the number of evaluable placebo-treated subjects.
Abbreviations: LDL-C=low-density lipoprotein cholesterol; mITT=modified intent-to-treat; SEM=standard error of the mean

Likewise, PCSK9 levels were reduced through Day 360 (mean reductions 33.4%, 36.5%, and 39.2% at 200 mg, 300 mg, and 500 mg inclisiran, respectively). PCSK9 levels were unaffected in the placebo group through Day 360.

**Figure 3.3.2.11: Percent Change from Baseline PCSK9 (ng/mL) by Dose Group over Time – mITT Population + Single Dose**




Source: Section 14.4, Figure 5.8.2.1
Note: Data for placebo-treated subjects are not presented beyond Day 210 since the majority of placebo-treated subjects did not have data collected beyond this timepoint. Data for the few placebo-treated subjects with PCSK9 values collected beyond Day 210 maybe be found in Section 14.2.2.2, Table 5.8.2.1 which includes the PCSK9 values along with the number of evaluable placebo-treated subjects.
Abbreviations: mITT=modified intent-to-treat; PCSK9=proprotein convertase subtilisin/kexin type 9; SEM=standard error of the mean

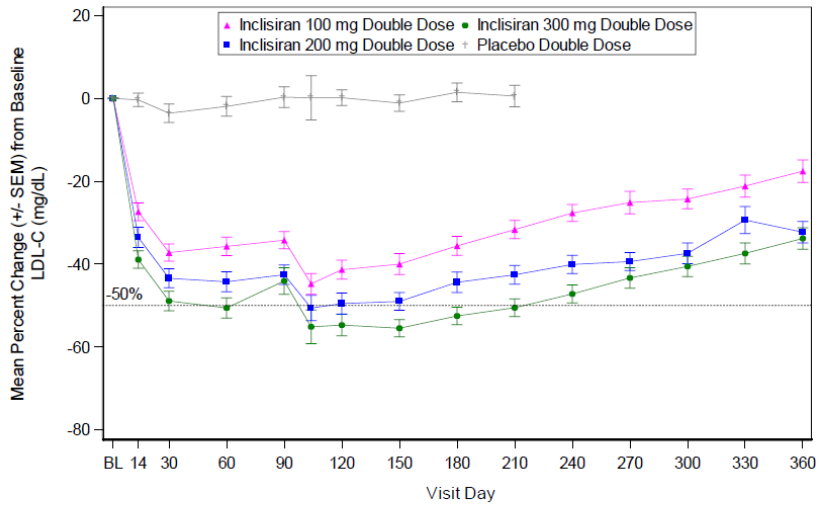
*Double dose group*

Results for the primary endpoint in the double dose groups of study Orion-1 showed a mean percentage LDL-C reduction of 35.5%, 44.9%, and 52.6% following two doses of 100 mg, 200 mg, and 300 mg inclisiran, respectively, compared to a 1.8% increase in the placebo group (all p<0.0001) for the mITT Population.

Results for the secondary endpoint percentage change in LDL-C from baseline to Days 30, 60, 90, 120, 150, and 180 showed LS mean reductions from baseline ranging from 34.09% to 40.99% with two doses of 100 mg, from 43.91% to 50.18% with two doses of 200 mg, and from 44.19% to 54.87% with two doses of 300 mg. In the placebo group, LS mean changes from baseline ranged between increases of 1.82% and decreases of 3.66% over time.

The maximum LS mean LDL-C reduction of 54.87% was observed at Day 150 following the administration of 300 mg inclisiran on Day 1 and Day 90. Although there was some return to group baseline values, the mean percent reduction from baseline at Day 360 after two doses of 100 mg was 17.6%, after two dose of 200 mg 32.3%, and after two dose of 300 mg 33.8%. In the placebo group, the mean percent reduction from baseline at Day 360 was 10.9%.

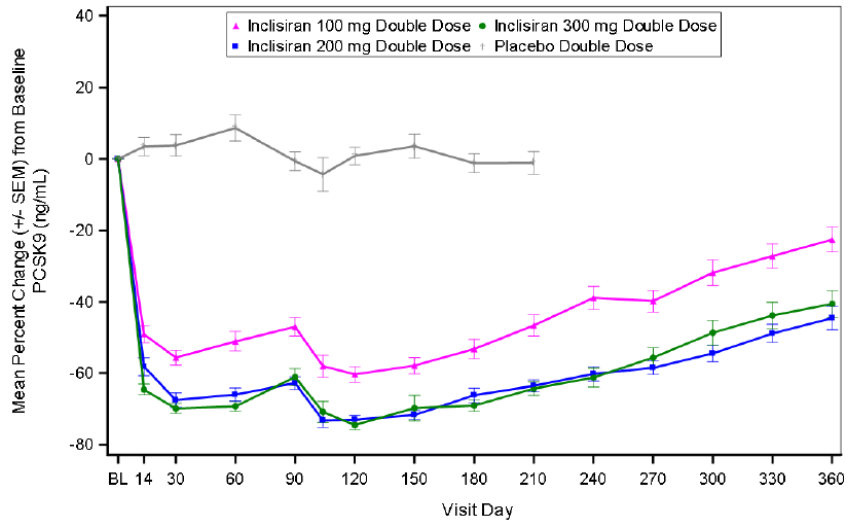
**Figure 3.3.2.12: Percent Change from Baseline Beta-Quantification LDL-C (mg/dL) by Dose Group over Time – mITT Population + Double Dose**




Source: Section 14.4, Figure 5.3.2.2
Note: Data for placebo-treated subjects are not presented beyond Day 210 since the majority of placebo-treated subjects did not have data collected beyond this timepoint. Data for the few placebo-treated subjects with beta-quantification LDL-C values collected beyond Day 210 maybe be found in Section 14.2.2.1, Table 5.4.2.2 which includes the beta-quantification LDL-C values along with the number of evaluable placebo-treated subjects.
Abbreviations: LDL-C=low-density lipoprotein cholesterol; mITT=modified intent-to-treat; SEM=standard error of the mean

PCSK9 levels were reduced through Day 360 (mean reductions of 22.6%, 44.6%, and 40.6% at doses of 100 mg, 200 mg, and 300 mg, respectively). PCSK9 levels were unaffected in the placebo group through Day 360.

**Figure 3.3.2.13: Percent Change from Baseline PCSK9 (ng/mL) by Dose Group over Time – mITT Population + Double Dose**




Source: Section 14.4, Figure 5.8.2.2
Note: Data for placebo-treated subjects are not presented beyond Day 210 since the majority of placebo-treated subjects did not have data collected beyond this timepoint. Data for the few placebo-treated subjects with PCSK9 values collected beyond Day 210 maybe be found in in Section 14.2.2.2, Table 5.8.2.2 which includes the PCSK9 values along with the number of evaluable placebo-treated subjects.
Abbreviations: mITT=modified intent-to-treat; PCSK9=proprotein convertase subtilisin/kexin type 9; SEM=standard error of the mean

The maximum reductions in PCSK9 and LDL-C observed in study ORION-1 were similar to the maximum reductions observed in study ALN-PCSSC-001, with both PCSK9 and LDL-C returning towards baseline slowly after the Day 90 dose. LDL-C lowering on Day 270 was similar to Day 90, suggesting a 6-month dosing regimen would be sufficient to maintain efficacy. The 300 mg dose given on Day 1 and Day 90 achieved a maximum LDL-C reduction of 56%, and had a greater effect than either the 100 mg or 200 mg doses. These results confirmed that less frequent doses of 300 mg inclisiran sodium are sufficient to achieve and maintain the PD response.

## Secondary pharmacology

Renal impairment

The safety, PK, and PD of inclisiran was studied in patients with mild, moderate, and severe renal impairment following administration of a single SC injection of 300 mg inclisiran in study ORION-7:

”A single-dose, open-label, parallel-group study to assess the pharmacokinetics of inclisiran in subjects with renal impairment compared to subjects with normal renal function”.

The primary objectives were to quantify the effect of different degrees of renal impairment on the PK of inclisiran and to assess safety and tolerability in order to develop dosing recommendations for subjects with renal impairment.

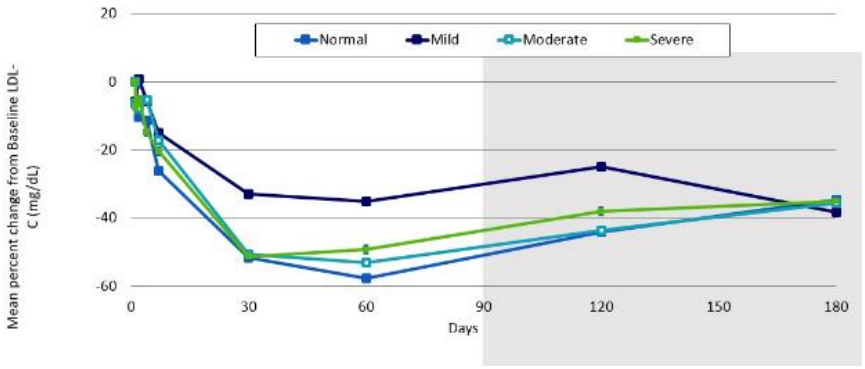
The secondary objective was to evaluate the effect of inclisiran on lipids, lipoproteins (TC, triglycerides, HDL-C, LDL-C calculated and measured by beta-quantification), and PCSK9 protein levels measured as a percentage of change from baseline.

Subjects were planned to be classified into 1 of the 4 groups: 3 groups with renal impairment (mild, moderate, severe impairment) as defined by their creatinine clearance (CrCl) and 1 group of healthy volunteers. The subjects with normal renal function received the study drug after the renal impaired subjects to ensure comparable average demographics regarding age, body weight, and proportional race and gender.

Reductions in the calculated LDL-C (mg/dL) were similar across all groups of renal function. The mean baseline LDL-C levels were 129.3, 142.9, 117.1, and 99.0 mg/dL in subjects with normal renal function and mild, moderate, and severe renal impairment, respectively. Reduction in the mean levels of calculated LDL-C was observed from 4 hours postdose on Day 1.

Reductions in the beta-quantification LDL-C (mg/dL) were similar across all groups of renal function. The mean baseline LDL-C levels were 135.7, 139.0, 112.9, and 95.4 mg/dL in subjects with normal renal function and with mild, moderate, and severe renal impairment, respectively. Reduction in the mean levels of beta-quantification LDL-C was observed from 4 hours postdose on Day 1.

**Figure 3.3.2.14: Mean Percent Change from Baseline Beta-Quantification LDL-C by Renal Function Group over Time**




It should be noted that the effect of inclisiran in subjects requiring haemodialysis on inclisiran PK has not been studied.

Hepatic impairment

The safety, PK, and PD of a single 300 mg SC injection of inclisiran sodium was studied in patients with mild and moderate hepatic impairment compared to matched controls in study ORION-6:

"A Phase I, open-label trial to evaluate the PK, PD, safety, and tolerability of a single dose of inclisiran administered subcutaneously in subjects with mild to moderate hepatic impairment compared to subjects with normal hepatic function".

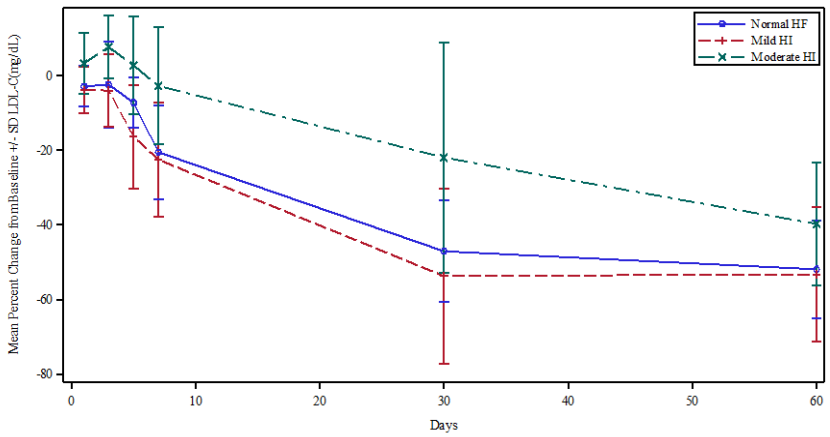
Subjects with normal hepatic function were dosed after dosing of hepatic impaired subjects in order to ensure comparable matching of subjects. Matched subjects with normal hepatic function were enrolled on a 1 to 1 basis and were not matched to more than 1 hepatically impaired subject within each hepatic function group.

Hepatic impairment subjects were classified at screening by hepatic function based on the Child-Pugh (CP) assessment. Scoring of CP assessment was repeated at check-in (Day 1).

Decreases in LDL-C from Baseline to Day 60 were reported for all groups. Subjects with moderate hepatic impairment had the lowest mean change (%) from baseline on Day 60.

Subjects with normal hepatic function and mild hepatic function had little changes in LDL-C between Day 30 and Day 60, whereas subjects with moderate hepatic impairment had a mean change from baseline of -22.0% and -39.7% on Day 30 and Day 60, respectively, suggesting that inclisiran may take longer to reach peak effectiveness in subjects with moderate hepatic impairment.

**Figure 3.3.2.15: Low-Density Lipoprotein Cholesterol (LDL-C), Mean Percent Change from Baseline ± SD by Hepatic Function Group over Time – PD Population**

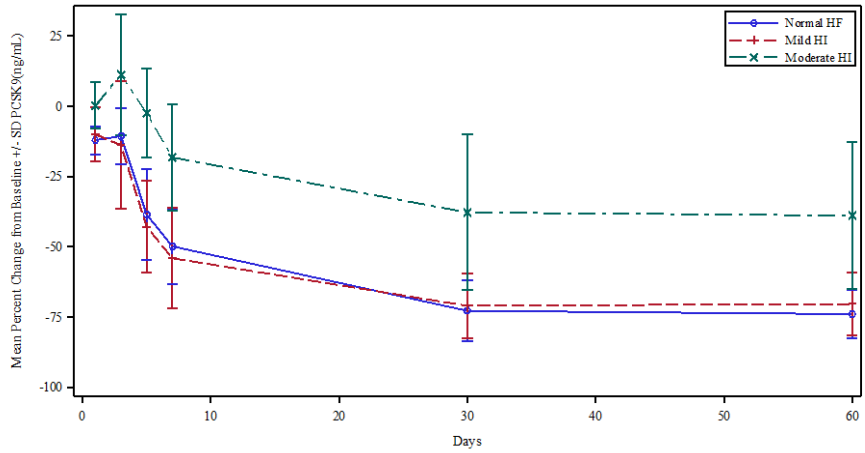



Source: Figure 14.5.2
Abbreviations: HF=hepatic function; HI=hepatic impairment; PD = pharmacodynamic; SD = standard deviation

Mean baseline PCSK9 was 327.9 ng/mL and 197.1 ng/mL for subjects with mild and moderate hepatic impairment (normal range 160 ng/mL to 521 ng/mL). Subject 133 had markedly higher PCSK9 at baseline compared to other subjects in the moderate group, which impacted baseline mean values and interpretation of data.

Decreases in PCSK9 from baseline to Day 60 were reported for all groups. The decrease was less pronounced in the group of subjects with moderate hepatic impairment. These subjects, particularly those with the highest CP score, had markedly lower mean PCSK9 levels at baseline compared to the subjects with mild or no hepatic impairment, which may account for the difference in effect. Within the group of subjects with moderate hepatic impairment, those with the greatest degree of impairment (CP score of 9) responded the least to inclisiran.

**Figure 3.3.2.16: PCSK9 Levels, Mean Percent Change from Baseline ± SD by Hepatic Function Group over Time – PD Population**



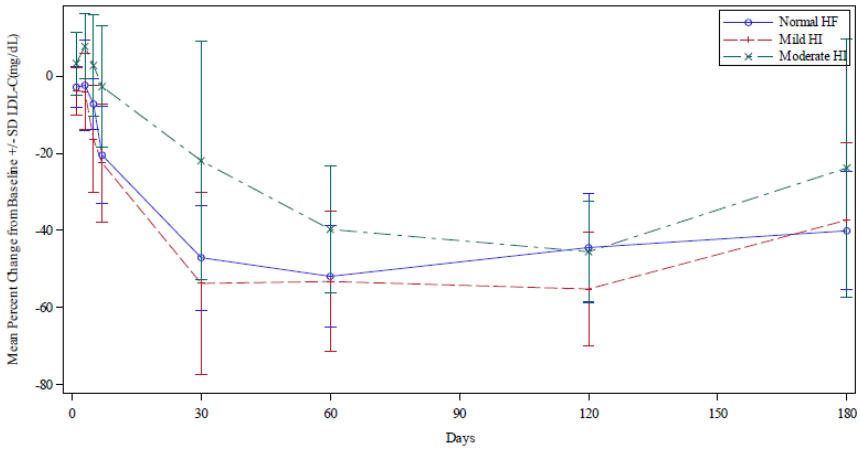

Source: Figure 14.5.4
Abbreviations: HF=hepatic function; HI=hepatic impairment; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamic; SD = standard deviation

Subjects with normal and mild hepatic impairment responded as expected to inclisiran in terms of LDL-C and PCSK9 reduction while the responses among subjects with moderate hepatic impairment varied. Subjects with a CP score of 9, who had low PCSK9 at baseline (Day 1), showed less reduction in PCSK9

and LDL-C, even with the exclusion of Subject 118, who had an increase in LDL-C. Subjects with a CP score of 7, who had normal PCSK9 at baseline, responded as expected with a mean reduction of PCSK9 of -59.5% and mean LDL-C reduction of 50.1%.

In the Day 60 to Day 180 addendum, where the results were presented up to Day 180, all subject groups had decreases in LDL-C on Day 180 compared to baseline. The greatest decreases were observed in subjects with mild hepatic impairment and normal hepatic function.

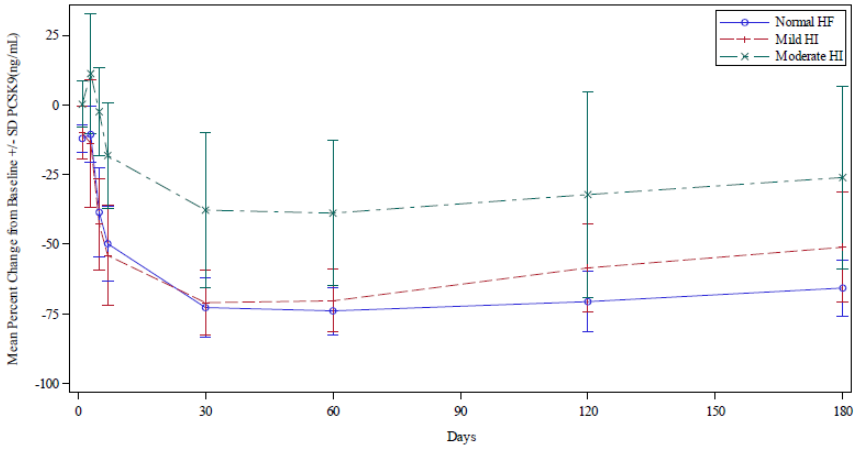
**Figure 3.3.2.17: Low-Density Lipoprotein Cholesterol (LDL-C), Mean Percent Change from Baseline ± SD by Hepatic Function Group over Time – PD Population**




Source: Figure 14.5.2
Abbreviations: HF = hepatic function; HI = hepatic impairment; PD = pharmacodynamic; SD = standard deviation

Decreases in PCSK9 from baseline to Day 180 were reported for all groups. The decrease was less pronounced in the group of subjects with moderate hepatic impairment. These subjects, particularly those with the highest CP score, had markedly lower mean PCSK9 levels at baseline compared to the subjects with mild or no hepatic impairment, which may account for the difference in effect.

**Figure 3.3.2.18: PCSK9 Levels, Mean Percent Change from Baseline ± SD by Hepatic Function Group over Time – PD Population**




Source: Figure 14.5.4
Abbreviations: HF = hepatic function; HI = hepatic impairment; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamic; SD = standard deviation

QT prolongation

The thorough QT study ORION-12 was a phase I randomised, double-blind, double-dummy, placebo- and positive-controlled, 3-way crossover study in healthy subjects with a supratherapeutic single SC injection of inclisiran 900 mg (3-fold the therapeutic dose), inclisiran placebo, and a single oral dose of moxifloxacin 400 mg (active control).

The primary objective was to assess the effect of a supratherapeutic dose of inclisiran on cardiac repolarisation as assessed by the QT interval corrected (QTc) for heart rate (HR) using the Fridericia correction (QTcF). Secondary objectives were to assess the effect of inclisiran on other electrocardiogram (ECG) parameters of HR, PR, RR, QRS, ST-, T-, and U-wave morphology, and QTc for HR using the Bazett correction if QTcF failed to adequately correct, to assess the effect on QTcF in relation to plasma levels of inclisiran using exploratory concentration-effect modelling, to evaluate the assay sensitivity using oral moxifloxacin as an active control, to evaluate the PK profile after a single dose of 900 mg inclisiran sodium, to evaluate the effect of inclisiran on PCSK9 and LDL-C, and to assess safety and tolerability in healthy subjects after a single dose of 900 mg inclisiran.

Following a supratherapeutic 900 mg dose of inclisiran sodium, the geometric mean $C_{max}$ was 2643 ng/mL (geometric CV% 43.6%) and occurred at a median $T_{max}$ of 4.003 hours postdose. The geometric mean $AUC_{0-24}$, $AUC_{0-48}$, $AUC_{0-t}$, and $AUC_{0-inf}$ were 34890 h*ng/mL, 38190 h*ng/mL, 37030 h*ng/mL, and 39,110 h*ng/mL, respectively. The geometric mean $t_{1/2}$ was 5.834 hours and geometric mean CL/F and Vd/F were 21.78 L/h and 183.3 L, respectively.

Observed QT was corrected for the influence of HR with the Fridericia formula. The adequacy of the correction formula was assessed by determining the linear relationship of QTcF to the RR interval (60,000 ÷ HR). Adequacy was defined as a population of QTcF: RR slope of <|0.045|, and a slope of <|0.045| in at least 50% of individual subjects. The prespecified criteria for adequacy of the correction were met.

The maximum predicted ddQTcF during the study, which occurred near $C_{max}$ at 4 hours, was 2.5 msec (90% CI 0.6, 4.5 msec) for inclisiran and 11.4 msec (90% CI 9.5, 13.4 msec) for moxifloxacin. Thus, inclisiran had no clinically significant effect on QTcF, while moxifloxacin had the expected substantial effect.

The dQTcF-plasma concentration relationship was assessed in an exploratory analysis to support the central tendency analysis. The model included dQTcF as the dependent variable and baseline QTcF, treatment, timepoint, and plasma concentration as independent variables. The dQTcF-concentration relationship was not statistically significant (p=0.0772). At the inclisiran mean $C_{max}$ observed in this study (2888 ng/mL), the model-predicted ddQTcF was 1.9 msec (90% CI 0.64, 3.17 msec). At the maximum individual inclisiran concentration observed in this study (8430 ng/mL), the model-predicted ddQTcF was 5.7 msec (90% CI 1.14, 10.27 msec). At the mean $C_{max}$ observed in a previous study (ORION-7) at the therapeutic dose of 300 mg in severe renal impairment (1760 ng/mL), the model-predicted ddQTcF was 1.1 msec (90% CI 0.34, 1.92 msec). Thus, inclisiran had no clinically significant effect on QTcF at systemic exposures that significantly exceeded those likely to be obtained at therapeutic doses.

No clinically significant group changes in QTcF, HR, PR interval, and QRS interval were observed, and there were no categorical values or change values of concern, and no pattern of drug effect except for the expected effect of moxifloxacin. Inclisiran appears to have no clinically or statistically significant effects on the ECG in humans at a supratherapeutic dose of 900 mg, 3-fold the therapeutic dose.

Exposure-response relationship in phase III studies

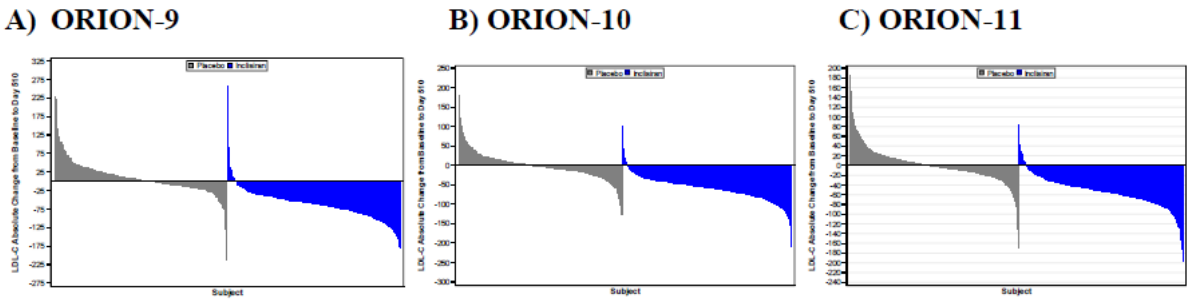
Similar exposure-response relationships as compared with the phase I study ALN-PCSSC-001 and the phase II study ORION-1 were observed in the 3 phase III studies, i.e. study ORION-9 conducted in subjects with HeFH, study ORION-10 conducted in subjects with ASCVD, and study ORION-11 conducted in subjects with ASCVD or ASCVD-risks equivalents.

Treatment with inclisiran 300 mg given by SC injection on Day 1, Day 90, and every 6 months thereafter resulted in 50 to 58% lowering of LDL-C relative to placebo at Day 510 and a time-averaged 44 to 54% lowering of LDL-C after Day 90 through Day 540 across the phase III studies and similar effects in PCSK9 reduction.

Inclisiran lowered Apo-B approximately 40%, supporting a mechanism of action of increased LDLR expression, lowered non-HDL and did not have any clinically significant impact on HDL-C or triglycerides.

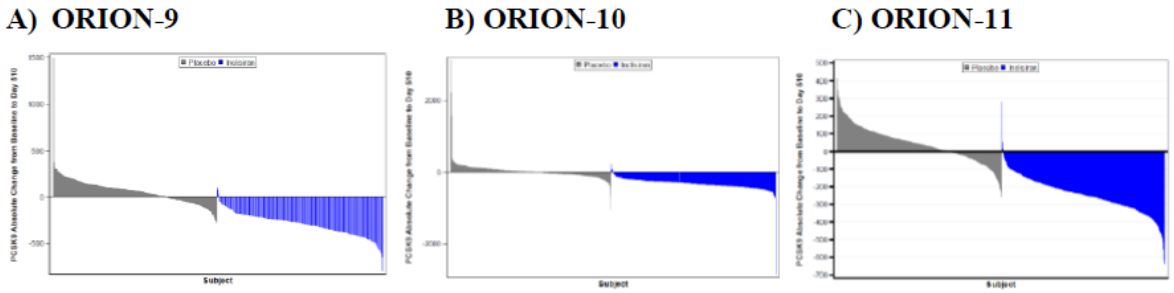
Inclisiran lowered LDL-C by -53.9% in patients not on statin (statin intolerant) and by –54.5% in patients on statin treatment.

**Figure 3.3.2.19: Waterfall Plots of Absolute Change in LDL-C from Baseline to Day 510: Three Confirmatory Phase III studies (ITT Population)**




Source: ORION-9 CSR Figure 14.2.3.1.2; ORION-10 CSR Figure 14.2.3.1.2; ORION-11 CSR Figure 14.2.3.1.2 Abbreviations: ITT=intent-to-treat; LDL-C=low-density lipoprotein cholesterol

**Figure 3.3.2.20: Waterfall Plots of Absolute Change from Baseline in PCSK9 at Day 510: Three Confirmatory Phase III studies (ITT Population)**




Source: ORION-9 CSR Figure 14.2.3.5.2; ORION-10 CSR Figure 14.2.3.5.2; ORION-11 CSR Figure 14.2.3.5.2 Abbreviations: ITT=intent-to-treat; PCSK9=proprotein convertase subtilisin/kexin type 9

PK/PD modelling

A population PD analysis was carried out evaluating PD profiles of PCSK9 and LDL-C levels after SC injection of inclisiran using a turnover model. The hypothetical liver effect compartment was linked to the synthesis rate for PCSK9 through an Imax model. PCSK9 levels were then linked to the degradation / clearance rate of LDL-C through the use of a second Imax model. Population PD analyses were based on available PD data (i.e., PCSK9 and LDL-C) from nine clinical trials, including 4 phase I studies, 2 phase II studies and 3 phase III studies (ALN-PCSSC-001, ORION-1, ORION-3, ORION-6, ORION-7, ORION-9, ORION-10, ORION-11, and ORION-12). Final model evaluation revealed a satisfactory model performance.

## 2.4.4. Discussion on clinical pharmacology

### Pharmacokinetics

No absolute bioavailability and human absorption, distribution, metabolism, and excretion (ADME) studies have been performed for inclisiran. Given these limitations, pharmacokinetics of inclisiran appear to have been overall sufficiently characterised. The applicant has not proposed any changes to the dosing recommendations in subjects with various stages of renal impairment as well as in subjects with mild and moderate hepatic impairment despite significant increases in exposures observed in these subjects as compared to healthy subjects. Given the infrequent and transient exposures to inclisiran that can be expected based on the long dosing interval (initially, after 3 months and then every 6 months), short t½ of inclisiran in plasma, and the lack of correlation with PD response, this may be considered acceptable from a PK point of view. However, as differences in the antisense to sense ratios have been noted in several subjects with renal impairment and the safety data in severe renal impairment is too limited to draw a final conclusion, inclisiran should be used with caution in patients with severe renal impairment.

### Pharmacodynamics

The mechanism of action that inclisiran blocks the natural pathway of RNA interference by binding intracellularly to the RISC appears reasonable. The cleaved PCSK9 mRNA is degraded and thus unavailable for protein translation, which results in decreased levels of the PCSK9 protein where 1 single blocked RISC can cleave many transcripts of the PCSK9 protein. This leads to a reduced degradation of the LDLR and thus to an increased removal of LDL-C.

Results of the phase I dose escalating study ALN-PCSSC-001 in healthy subjects and the phase II single and multiple dose study ORION-1 in subjects with ASCVD or ASCVD-risk equivalents and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapy showed robust and significant reductions in PCSK9 levels with concomitant reductions in LDL-C levels after inclisiran treatment. Results of both studies showed an optimal effect on PCSK9 and LDL-C with an inclisiran 300 mg SC injection and study ORION-1 demonstrated that every 6 months dosing would be the optimal dosing regimen to maintain a time adjusted average LDL-C reduction of greater than 50% over 6 months.

Based on these observations, the optimal dose regimen for the phase III trials was determined to be 300 mg inclisiran sodium administered SC on Day 1, Day 90, and every 6 months thereafter.

Results of the phase I / phase II studies ORION-6 and ORION-7 demonstrated that the LDL-C reduction follows the decrease of PCSK9 over time, that the reduction of the PD parameters was comparable over the different renal impairment groups, and that PCSK9, LDL-C, and TC levels decreased in all hepatic impairment groups from baseline to Day 180 with less pronunciation in the moderate hepatic impairment group. According to the results of these studies no dose adjustments of inclisiran seems to be necessary across the different renal and hepatic impairment groups; however, no data are available for subjects on haemodialysis and with severe hepatic impairment and end stage liver disease.

The thorough QT study ORION-12 indicated an absence of effect of inclisiran on potential QTc prolongation. No indication for a QT prolonging effect of inclisiran was observed after dosing with a 900 mg dose and no need for closer QT observation during the phase III studies was raised.

## 2.4.5. Conclusions on clinical pharmacology

No absolute bioavailability and human absorption, distribution, metabolism, and excretion (ADME) studies have been performed for inclisiran. Given these limitations, pharmacokinetics of inclisiran have been sufficiently characterised.

The mode of action of inclisiran has been established reasonably well and LDL-C lowering has been demonstrated. There is no sign of a pro-arrhythmic effect of inclisiran. The effect on LDL-C has been further explored with a PK/PD model. The pharmacology effects were mainly evaluated based on the effect on PCSK9 and LDL-C lowering. This approach is supported, as it is the primary relevant marker for pharmacology and efficacy of inclisiran in relation to any potential cardiovascular effect. The LDL-C lowering effect was demonstrated in a phase I study in healthy volunteers and in a phase II study in subjects with ASCVD or ASCVD-risk equivalents. The PCSK9 and LDL-C percentage reduction from baseline was dose dependent up to 300 mg inclisiran with no further benefit of higher doses.

Studies in subjects with renal or hepatic impairment indicated that the LDL-C reduction follows the decrease of PCSK9 over the time in all examined groups of renal and hepatic impairment and that a dose reduction in the groups investigated is not necessary. However, since safety data in severe renal impairment is too limited to draw a definite conclusion, inclisiran should be used with caution in patients with severe renal impairment. Results of a thorough QT study indicated an absence of effect of inclisiran on potential QTc prolongation.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response studies

The inclisiran clinical development programme included 4 phase I studies, 3 phase II studies (1 still ongoing), and 6 phase III studies (3 still ongoing).

The dose-response effect was evaluated in the phase I study ALN-PCSSC-001 and the phase II study ORION-1 including either healthy subjects with elevated LDL-C concentrations or subjects with ASCVD or ASCVD-risk equivalents with or without statin co-medication. A PCSK9 and in consequence LDL-C lowering effect was observed with inclisiran doses of 25 to 800 mg. Reductions in PCSK9 and LDL-C levels were apparent within 14 days post dosing, with mean reductions of 71% to 74% for PCSK9 and 48% to 51% for LDL-C observed 30 to 60 days post 300 mg dose.

According to the phase I/II results, the optimal dose for the phase III trials with a maximum reduction in LDL-C seemed to be 300 mg inclisiran administered at days 1 and 90, and every 180 days thereafter.

### 2.5.2. Main studies

The primary efficacy data obtained in the proposed target population were derived from the pivotal phase III studies ORION-9, ORION-10, and ORION-11. The 3 confirmatory studies were placebo-controlled, double-blind, randomised trials in patients with HeFH or ASCVD or ASCVD-risk equivalents with elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapy. Additional supportive efficacy data come from the ongoing open-label extension study ORION-3 and the long-term studies ORION-4 in subjects with ASCVD, ORION-5 in subjects with HoFH, and ORION-8 in subjects with ASCVD, ASCVD-risk equivalents (e.g., diabetes and FH), HeFH, or HoFH.

Study reports from the long-term studies ORION-4, ORION-5, and ORION-8 have not been included in the dossier.

# ORION-9, ORION-10, ORION-11

The applicant conducted 3 confirmatory studies (ORION-9, ORION-10, ORION-11) as placebo-controlled, double-blind, randomised trials to evaluate the effect of 300 mg of inclisiran sodium given as SC injections in subjects with a history of HeFH with a diagnosis of HeFH by genetic testing or documented uncontrolled LDL-C levels >190 mg/dL (study ORION-9) and in subjects with ASCVD and ASCVD-risk equivalent (studies ORION-10 and ORION-11), despite maximally tolerated statin therapy. Inclisiran sodium 300 mg was given by SC injection on Day 1, Day 90, and every 6 months thereafter.

## *Methods*

The 3 completed confirmatory studies ORION-9, ORION-10, and ORION-11 were double-blind, placebo-controlled, randomised, parallel-group, multicentre studies with injections of inclisiran sodium 300 mg s.c. or placebo on Days 1, 90, and every 180 days thereafter in adult patients who are at risk of CVD when used alone and in combination with HMG-CoA reductase inhibitors (statins) or ezetimibe.

In each study, the co-primary efficacy endpoints were 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

To evaluate the efficacy of inclisiran as an add-on to lipid-modifying therapy subjects were required to be on a background of maximally tolerated statin therapy before randomisation with or without other LDL-C lowering agents such as ezetimibe. Subjects not receiving statins must have had documented evidence of intolerance to all doses of at least 2 different statins. Subjects were randomised (1:1) to either inclisiran sodium 300 mg s.c. injection or placebo, stratified by current use of statins or other lipid-modifying therapies. Subjects randomised in ORION-9 and ORION-11 were also stratified by country.

Screening occurred approximately 2 weeks prior to Day 1 (Visit 1). Patients who met all enrolment criteria during the screening period were instructed to continue their therapy(ies) for lipid lowering and to maintain consistent diet and exercise patterns throughout the study.

The reduction of LDL-C as a causal factor in the pathophysiology of ASCVD with strong and consistent evidence from genetic studies, prospective epidemiologic cohort studies, Mendelian randomization studies, and randomised intervention trials was chosen as surrogate marker.

## *Study Participants*

The 3 phase III studies included 3660 subjects with 18 months duration and tested 2 product presentations – namely 'vial and syringe' and 'prefilled syringe', of which the latter is proposed in this application.

**Important inclusion criteria** in the 3 confirmatory studies included a history of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented history of untreated LDL-C of >190 mg/dL, and a family history of FH, elevated cholesterol or early heart disease may indicate FH, stable on a low-fat diet (e.g., National Cholesterol Education Program), serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) at screening and calculated glomerular filtration rate (GFR) >30 mL/min by estimated glomerular filtration rate (eGFR) using standardised clinical methodology (study ORION-9); a history of ASCVD (CHD, CVD, or PAD), serum LDL-C ≥1.8 mmol/L (≥70 mg/dL), and no current or planned renal dialysis or renal transplantation (study ORION-10); a history of ASCVD (CHD, CVD, or PAD) or ASCVD-risk equivalents (type 2 diabetes, FH, and including subjects whose 10-year risk of a CV event assessed by Framingham Risk Score or equivalent has a target LDL-C of <100 mg/dL), serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) for ASCVD subjects or ≥2.6 mmol/L (≥100 mg/dL) for ASCVD-risk equivalent subjects at screening and calculated GFR >30 mL/min by eGFR using standardised clinical methodology (study ORION-11).

**Additional inclusion criteria** common in all 3 studies were fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening and subjects on statins should have been receiving a maximally tolerated dose. Maximum tolerated dose was defined as the maximum dose of statin that can be taken on a regular basis without intolerable AEs. Intolerance to any dose of any statin was documented as historical AEs attributed to the statin in question in the source documentation and on the Medical History page of the electronic case report form (eCRF) and subjects not receiving statin must have had documented evidence of intolerance to all doses of at least 2 different statins.

**Exclusion criteria** were related to any uncontrolled or serious disease, or any medical or surgical condition that could either interfere with participation in the clinical study and/or put the subject at significant risk (according to investigator's [or delegate] judgement) if he/she participated in the clinical study and to underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate), may have interfered with interpretation of the clinical study results, and major adverse CV event within 3 months prior to randomisation.

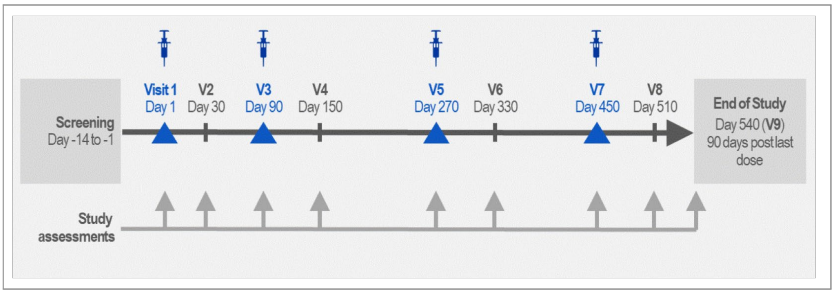
## *Treatments*

With respect to **background LMT** in all 3 confirmatory studies subjects were allowed to be on hormone replacement therapy, on lipid-lowering medications as subjects already on a stable (≥30 days before screening) lipid-lower medications (such as statins and/or ezetimibe) should remain on the dose that they had received during participation in the original protocol unless clinically indicated, prescription medications prescribed to treat preexisting medical conditions such as diabetes and hypertension, and prescription or non-prescription medications, when necessary to treat an AE, and at the discretion of the investigator.

Subjects were not allowed to add medications prescribed to lower LDL-C (e.g., statins, ezetimibe, lomitapide, mipomersen, niacin, colesevelam, bile acid absorption inhibitors, monoclonal antibodies directed towards PCSK9) and any medication taken for the purpose of lipid lowering, including over-the-counter or herbal therapies during the studies.

All 3 phase III studies had similar designs to facilitate data pooling – including objectives, endpoints, placebo control, test medication dosage, the schedule and sequence of study procedures (set up to capture peak and trough effects of inclisiran), protocol assessments, adverse event reporting, data collection, statistical methods, and quality management and included a screening period of 14 days. The same design scheme applies to ORION-9, ORION-10, and ORION-11.

**Figure 3.3.5.10: Common design of the 3 Phase III Studies**




Inclisiran was to be administered on Day 1, Day 90, Day 270, and Day 450 in all 3 studies and no dose adjustments occurred during the treatment periods.

## *Objectives*

The co-primary and secondary objectives of these studies were to evaluate the efficacy of inclisiran as compared to placebo on the 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

## *Outcomes/endpoints*

Primary endpoint

Each of the 3 pivotal Phase 3 studies assessed percent change in LDL-C from baseline to Day 510 and the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 as the co-primary efficacy endpoints. A cardiovascular outcomes trial of inclisiran versus placebo in 15,000 ASCVD subjects is ongoing and results are anticipated in 2024.

Secondary endpoints

The secondary endpoints of the studies were:

- Absolute change in LDL-C from baseline to Day 510

- Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540
- Percentage change from baseline to Day 510 in PCSK9, total cholesterol, apolipoprotein B (Apo-B), and non-HDL-C.

## *Sample size*

For all 3 pivotal phase 3 studies the sample size calculation was performed with the assumption (which was based on the observed results from a Phase II study) that the difference in change from baseline between the active dose group and the placebo group for LDL-C would be no less than 30 mg/dL, with a standard deviation of 20 mg/dL.

- **Study ORION-9**

Assuming about a 5% drop out rate, the sample size was approximately 380 subjects that were evaluable for efficacy across the placebo and inclisiran dose groups. This sample size of at least 380 evaluable subjects, provided more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at 1-sided significance level of 0.025. Due to faster than expected enrollment, actual enrollment was 482 subjects. This increased sample size contributed additional safety data and did not appreciably affect power calculations.

- **Study ORION-10**

Assuming about a 5% drop out rate, the sample size was planned to be approximately 1425 subjects that were evaluable for efficacy across the placebo and inclisiran dose groups. This sample size of at least 1425 evaluable subjects, was expected to provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at 1-sided significance level of 0.025. This sample size also contributed additional sufficient safety data.

- **Study ORION-11**

Assuming about a 5% drop out rate, the sample size would be approximately 1425 subjects that were evaluable for efficacy across the placebo and inclisiran dose groups. This sample size of at least 1425 evaluable subjects, would provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at one-sided significance level of 0.025. This sample size would also contribute additional sufficient safety data.

## *Randomisation*

In the confirmatory phase 3 studies, subjects were required to be on a background of maximally tolerated statin therapy before randomisation with or without other LDL-C lowering agents such as ezetimibe. Subjects were randomised (1:1) to either inclisiran sodium 300 mg or placebo on Day 1, Day 90, Day 270, and Day 450, stratified by current use of statins or other lipid-modifying therapies. Subjects randomised in ORION-9 and ORION-11 were also stratified by country.

## *Blinding (masking)*

In all 3 studies the study drug was blinded prior to distribution to the site. Each study drug vial, inclisiran or placebo, contained a yellow shroud to blind the vial. Randomisation via an automated IRT was used to assign subjects to blinded study drug. The clinical study site pharmacist maintained the double-blind according to site-specific procedures and the Pharmacy Manual. As inclisiran may be visually distinguishable from placebo, blinded syringes were provided to all study sites and used to maintain the blind.

## *Statistical methods*

The Statistical methods of the 3 pivotal studies are similar. Efficacy evaluations were primarily based on the Intent-to-Treat (ITT) population containing all randomised subjects according to their randomised allocation. Additional analysis were conducted based on the Full-Analysis-Set (FAS) population (all randomised subjects receiving treatment at least once) and the modified ITT population (all subjects in the FAS having available LDL-C measurements at baseline and Day 510).

*Missing data handling*

The sponsor diligently followed up with each subject during the study on all efficacy laboratory assessments to keep missing data to a minimum regardless of whether the subject was on study treatment, used ancillary therapies, experienced an adverse event, or adhered to the protocol, and all data were included in all analyses. Although the studies did not employ the estimand framework discussed in the addendum to ICH E9 R1(*EMA/CHMP/ICH/436221/2017*), this follow-up of patients is in line with targeting an estimand based on the treatment policy strategy, which is considered of regulatory relevance in this setting.

If missing data, defined as data not available from either scheduled (within the protocol defined visit window) or unscheduled visits, occurred for the primary or any of key secondary efficacy endpoints then that data were multiply imputed (total of 100 imputations). Percentage changes and absolute changes were calculated after imputation. Two different approaches were used for the two co-primary endpoints, but both approaches impute missing data under the assumption that the outcome would have been similar to those in the placebo group with similar background characteristics. This is in principle acceptable and aligned to a treatment policy strategy.

More specifically, the primary method to impute missing data for the first co-primary efficacy endpoint (percentage change in LDL-C from baseline to Day 510) was a multiple imputation washout model. For subjects in the inclisiran group only missing Day 510 values will be imputed based on placebo data and accounting for the subjects' baseline value and use of statin/lipid-modifying therapy (LMT) at baseline. For subjects in the placebo arm missing data for all visits are imputed and the applied imputation approach corresponds to imputing based on the missing-at-random (MAR) assumption in this arm. This washout model was used in ORION-11. A modified washout model was used in ORION-9 and -10, in the integrated efficacy analysis and as a post-hoc analysis in ORION-11. This modified version deviates from the described washout model by imputing intermittent missing Day 510 measurement in the inclisiran arm based on the MAR assumption (i.e. based on observed inclisiran data instead of placebo data) for subjects who received all 4 inclisiran doses, had the Day 510 value missing, and had evaluable data at Day 540.

The primary method to impute missing data for the second co-primary endpoint (time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540) used a control-based pattern-mixture model (PMM). For subjects who discontinued the study without any further follow-up data, missing data for all visits were imputed based on placebo data (for inclisiran and placebo). Intermittent missing values will be imputed based on the MAR assumption.

The amount of missing data and consequently its impact on study results and conclusions is, overall, very low. Furthermore, the control-based pattern-mixture model used for the second co-primary efficacy endpoint is also used as a sensitivity analysis for the first co-primary endpoint and results are similar.

Missing data for key secondary endpoints will be imputed using the control-based PMM. Missing data for all parameters not listed in the primary and key secondary endpoints were not imputed and were excluded from the associated analysis.

In addition, sensitivity analyses using different missing data handling (see below) were performed on co-primary and key secondary efficacy endpoints to assess the impact of missing values.

*Analysis of Co-Primary Endpoints*

For percentage change in LDL-C from baseline to Day 510, an analysis of covariance (ANCOVA) model is applied to each of the 100 multiply imputed datasets. The model included a fixed effect for treatment and baseline LDL-C as a covariate.

For time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540, a mixed-effects model for repeated measurements (MMRM) including fixed effects for treatment, visit, baseline value, and the interaction between treatment and visit is applied to each of the 100 multiply imputed datasets. The Restricted Maximum Likelihood (REML) estimation approach will be used with the covariance structure set as "Unstructured". The time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 and its difference between treatments was calculated from the MMRM by means of linear combinations of the estimated means after Day 90 and up to Day 540. Note that Day 90 was excluded from the MMRM.

For each endpoint, treatment effects from the 100 analyses will be combined using Rubin's Rules and the difference in the least squares means between treatment groups and corresponding two-sided 95% confidence interval will be provided for hypothesis testing.

For Orion-11, ANCOVA and MMRM analysis used to evaluate co-primary endpoints were extended by a fixed effect for current use of statins or other LMT at baseline. However, additional post-hoc analyses were conducted excluding this covariate.

A number of sensitivity analyses were conducted for both co-primary endpoints including analysis that account for stratification factors and analyses that assess the impact of missing data. Analyses for the latter include MMRM analyses without missing data imputation (i.e. based on the missing-at-random assumption) and tipping-point analyses evaluating how strong deviations from missing-at-random assumption need to be to lose statistical significance. Furthermore, the control-based pattern-mixture model will also be applied for the first co-primary endpoint. Overall, these analyses are supported and show robustness of result. Tipping-points calculated generally correspond to a worsening way beyond the patients' baseline levels and further support robustness.

Efficacy data were also analysed for relevant subgroups.

*Analyses of Secondary Endpoints*

The absolute change in LDL-C from baseline to Day 510 and percentage change from baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C will be analysed using a MMRM with covariates as specified for the second co-primary endpoint on each of the multiply imputed data sets. Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 will be analysed similarly to the second co-primary endpoint. MMRM without multiple imputation will be used as sensitivity analyses for the key secondary endpoints.

Other secondary endpoints will be analysed based on available data. The two-sided 95% confidence interval for least squares means will be provided for continuous variables at a single timepoint using an analysis of covariance model or using MMRM methods for variables measured over time. The odds ratio and 95% confidence interval for the odds ratio will be provided for binary variables using logistic regression models. Nominal p-values will be provided when applicable.

*Multiplicity Control*

Both co-primary efficacy endpoints were tested hierarchically at a two-sided alpha level of 5% and not in the usual sense of 'co-primary' endpoints (meaning both endpoints need to show statistical

significance for study success). Nevertheless, hierarchical testing properly controls the type 1 error and, in the end, superiority over placebo could be shown for both endpoints.

In case superiority can be achieved for both co-primary endpoints, key secondary endpoints were tested and multiplicity was controlled across these key secondary endpoints using Hochberg procedure. The study reports do not explicitly discuss the application of the Hochberg procedure. However, as all p-values for primary and key secondary endpoints are <0.0001, it is directly apparent that superiority can be claimed for all these endpoints based on the specified multiplicity control strategy. Generally, also adjusted p-values should be provided. These are currently not available, but - given that all p-values are <0.0001 - adjusted p-values will also be <0.0001.

*Changes in the conduct of analysis*

For each study, some aspects of the statistical analysis were changes after unblinding of the studies. For ORION-11, additional post-hoc analyses were conducted using the modified washout model for the first co-primary endpoint and analyses excluding the effect of use of statins/LMT at baseline from efficacy analysis. This can be agreed. In contrast, for ORION-9 and -10, accounting for ‚use of statins/LMT at baseline' in the imputation models resulted in convergence issues for all or some of the primary and key secondary efficacy endpoints and the effect was excluded from the imputation model. In principle, this results in lack of proper pre-specification of the imputation approach. Still, the amount of missing data is low and the number of different sensitivity analyses using different assumptions to handle missing data have been conducted showing that results are robust and not relevantly impacted by missing data. Hence, this issue is not considered of further concern.

*Integrated Summary of Efficacy*

The primary analysis of efficacy is based on data from each study individually. Pooled analyses were performed for these studies as follows: Efficacy Pool 1, includes all 3 Phase III trials, ORION-9, ORION-10, and ORION-11 and Efficacy Pool 2, includes only ORION-10 and ORION-11, since ORION-9 includes subjects with HeFH who have different demographic (e.g., younger age) and disease profiles.

Analysis is similar to the one described above for the individual studies except that analysis model include an additional fixed effect for study.

## *Results*

### *Baseline data*

Major baseline characteristics for the 3 studies are presented in the table below.

**Table 3.3.5.1: Demographics and Baseline Characteristics in the Controlled Phase III Studies – ITT-Population; N = 3660**

| Demographic Characteristics | ORION-9 | | | ORION-10 | | | ORION-11 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo N=240 | Inclisiran N=242 | Total N=482 | Placebo N=780 | Inclisiran N=781 | Total N=1561 | Placebo N=807 | Inclisiran N=810 | Total N=1617 |
| **Age at Informed Consent (years)** | | | | | | | | | |
| Mean ± SD | 55.0±11.81 | 54.4±12.48 | 54.7±12.14 | 65.7±8.89 | 66.4±8.90 | 66.0±8.90 | 64.8±8.68 | 64.8±8.29 | 64.8±8.48 |
| **Age Categories (years) n (%)** | | | | | | | | | |
| 18 - <65 | 185 (77.1) | 189 (78.1) | 374 (77.6) | 333 (42.7) | 297 (38.0) | 630 (40.4) | 366 (45.4) | 367 (45.3) | 733 (45.3) |
| ≥65 | 55 (22.9) | 53 (21.9) | 108 (22.4) | 447 (57.3) | 484 (62.0) | 931 (59.6) | 441 (54.6) | 443 (54.7) | 884 (54.7) |
| 18 - <75 | 233 (97.1) | 234 (96.7) | 467 (96.9) | 649 (83.2) | 638 (81.7) | 1287 (82.4) | 693 (85.9) | 721 (89.0) | 1414 (87.4) |
| ≥75 | 7 (2.9) | 8 (3.3) | 15 (3.1) | 131 (16.8) | 143 (18.3) | 274 (17.6) | 114 (14.1) | 89 (11.0) | 203 (12.6) |
| **Gender n (%)** | | | | | | | | | |
| Male | 115 (47.9) | 112 (46.3) | 227 (47.1) | 548 (70.3) | 535 (68.5) | 1083 (69.4) | 581 (72.0) | 579 (71.5) | 1160 (71.7) |
| Female | 125 (52.1) | 130 (53.7) | 255 (52.9) | 232 (29.7) | 246 (31.5) | 478 (30.6) | 226 (28.0) | 231 (28.5) | 457 (28.3) |
| **Weight (kg)**** | | | | | | | | | |
| N | 240 | 242 | 482 | 779 | 781 | 1560 | 806 | 810 | 1616 |
| Mean ± SD | 84.2±18.27 | 83.7±18.55 | 83.9±18.39 | 93.6±21.57 | 92.2±19.60 | 92.9±20.61 | 87.6±18.19 | 85.8±16.24 | 86.7±17.26 |
| **Height (cm)**** | | | | | | | | | |
| N | 240 | 242 | 482 | 780 | 781 | 1561 | 806 | 810 | 1616 |
| Mean ± SD | 170.5±10.14 | 169.8±11.10 | 170.2±10.63 | 171.3±10.10 | 171.0±10.55 | 171.1±10.33 | 169.8±9.25 | 169.7±9.43 | 169.8±9.34 |

| Demographic Characteristics | ORION-9 | | | ORION-10 | | | ORION-11 | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Placebo N=240** | **Inclisiran N=242** | **Total N=482** | **Placebo N=780** | **Inclisiran N=781** | **Total N=1561** | **Placebo N=807** | **Inclisiran N=810** | **Total N=1617** |
| **BMI (kg/m²)**** | | | | | | | | | |
| N | 240 | 242 | 482 | 779 | 781 | 1560 | 806 | 810 | 1616 |
| Mean ± SD | 28.8±5.09 | 29.0±5.68 | 28.9±5.39 | 31.8±6.44 | 31.5±6.25 | 31.7±6.35 | 30.2±5.15 | 29.7±4.79 | 30.0±4.98 |
| **Waist Circumference (cm)**** | | | | | | | | | |
| N | 239 | 241 | 480 | 775 | 780 | 1555 | 805 | 810 | 1615 |
| Mean ± SD | 98.4±13.99 | 98.6±14.84 | 98.5±14.41 | 107.5±15.67 | 107.3±14.32 | 107.4±15.00 | 103.5±13.50 | 102.3±12.76 | 102.9±13.14 |
| **Race n/N (%)** | | | | | | | | | |
| American Indian or Alaska | 0 (0.0) | 1 (0.4) | 1 (0.2) | 4 (0.5) | 2 (0.3) | 6 (0.4) | 0 (0.0) | 1 (0.1) | 1 (0.1) |
| Native | | | | | | | | | |
| Asian | 5 (2.1) | 7 (2.9) | 12 (2.5) | 1 (0.1) | 9 (1.2) | 10 (0.6) | 2 (0.2) | 6 (0.7) | 8 (0.5) |
| Black or African American | 7 (2.9) | 8 (3.3) | 15 (3.1) | 87 (11.2) | 110 (14.1) | 197 (12.6) | 8 (1.0) | 12 (1.5) | 20 (1.2) |
| Native Hawaiian or Other | 1 (0.4) | 0 (0.0) | 1 (0.2) | 3 (0.4) | 7 (0.9) | 10 (0.6) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| Pacific Islander | | | | | | | | | |
| White | 227 (94.6) | 226 (93.4) | 453 (94.0) | 685 (87.8) | 653 (83.6) | 1338 (85.7) | 796 (98.6) | 791 (97.7) | 1587 (98.1) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Ethnicity n/N (%)** | | | | | | | | | |
| Hispanic or Latino | 8 (3.3) | 7 (2.9) | 15 (3.1) | 104 (13.3) | 108 (13.8) | 212 (13.6) | 4 (0.5) | 5 (0.6) | 9 (0.6) |
| Not Hispanic or Latino | 232 (96.7) | 235 (97.1) | 467 (96.9) | 676 (86.7) | 673 (86.2) | 1349 (86.4) | 803 (99.5) | 805 (99.4) | 1608 (99.4) |

| Demographic Characteristics | ORION-9 | | | ORION-10 | | | ORION-11 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo N=240 | Inclisiran N=242 | Total N=482 | Placebo N=780 | Inclisiran N=781 | Total N=1561 | Placebo N=807 | Inclisiran N=810 | Total N=1617 |
| **Country n (%)** | | | | | | | | | |
| Canada | 11 (4.6) | 12 (5.0) | 23 (4.8) | 0 (0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Czech Republic | 5 (2.1) | 7 (2.9) | 12 (2.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 11 (1.4) | 10 (1.2) | 21 (1.3) |
| Denmark | 26 (10.8) | 23 (9.5) | 49 (10.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Germany | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 41 (5.1) | 42 (5.2) | 83 (5.1) |
| Hungary | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 52 (6.4) | 52 (6.4) | 104 (6.4) |
| Netherlands | 19 (7.9) | 19 (7.9) | 38 (7.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Poland | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 357 (44.2) | 360 (44.4) | 717 (44.3) |
| Spain | 42 (17.5) | 42 (17.4) | 84 (17.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Sweden | 16 (6.7) | 18 (7.4) | 34 (7.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| United Kingdom | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 231 (28.6) | 231 (28.5) | 462 (28.6) |
| United States | 32 (13.3) | 33 (13.6) | 65 (13.5) | 780 (100.0) | 781 (100.0) | 1561 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ukraine | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 54 (6.7) | 55 (6.8) | 109 (6.7) |
| South Africa | 89 (37.1) | 88 (36.4) | 177 (36.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 61 (7.6) | 60 (7.4) | 121 (7.5) |
| **Baseline GFR (mL/min/1.73m$^2$)**** | | | | | | | | | |
| Mean ± SD | 83.8±19.33 | 86.3±20.41 | 85.1±19.90 | 76.1±22.05 | 75.6±22.27 | 75.8±22.15 | 79.1±19.54 | 80.0±19.23 | 79.6±19.38 |
| **Baseline GFR Category n (%)** | | | | | | | | | |
| ≥15 - <30 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (0.9) | 10 (1.3) | 17 (1.1) | 2 (0.2) | 1 (0.1) | 3 (0.2) |

| Demographic Characteristics | ORION-9 | | | ORION-10 | | | ORION-11 | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Placebo N=240** | **Inclisiran N=242** | **Total N=482** | **Placebo N=780** | **Inclisiran N=781** | **Total N=1561** | **Placebo N=807** | **Inclisiran N=810** | **Total N=1617** |
| ≥30 - <60 | 20 (8.3) | 17 (7.0) | 37 (7.7) | 169 (21.7) | 170 (21.8) | 339 (21.7) | 98 (12.1) | 108 (13.3) | 206 (12.7) |
| ≥60 - <90 | 138 (57.5) | 131 (54.1) | 269 (55.8) | 414 (53.1) | 422 (54.0) | 836 (53.6) | 482 (59.7) | 459 (56.7) | 941 (58.2) |
| ≥90 | 82 (34.2) | 94 (38.8) | 176 (36.5) | 190 (24.4) | 179 (22.9) | 369 (23.6) | 225 (27.9) | 242 (29.9) | 467 (28.9) |

** This number is based on the number of subjects who answered the question on the eCRF.

Abbreviations: BMI=body mass index; GFR=glomerular filtration rate; SD=standard deviation

Most of the participants in the 3 confirmative studies were on a lipid-modifying therapy at baseline. LMT usage was generally balanced between the treatment groups at randomization (Day 1).

In study ORION 9, 94.4% (455/482) of subjects received LMT, 90.5% (436/482) of subjects received statin therapy, and 55.4% (267/482) received other LMT (58.3%; 140/240 of placebo-treated subjects and 52.5%; 127/242 of inclisiran-treated subjects) and 3.9% (19/482) received other LMT and no statin.

Overall, 73.9% (356/482) were on a high intensity statin at baseline. A total of 14.5% (70/482) of subjects received a moderate intensity statin and 1.9% (9/482) subjects received a low intensity statin at baseline. Approximately half (52.3%; 252/482) of subjects were treated with ezetimibe.

A total of 25.3% (122/482) of subjects were either partially or completely intolerant to statins. The most common symptoms of statin intolerance (partial or complete) were muscle ache (74.6%; 91/122), other symptoms (36.1%; 44/122), and cramping (22.1%; 27/122).

In study ORION-10, 94.7% (1478/1561) of subjects received LMT, 89.2% (1393/1561) of subjects received statin therapy, and 31.3% (489/1561) received other LMT.

Two-thirds (69.4%; 1084/1561) of subjects were on a high intensity statin at baseline. A total of 18.7% (292/1561) of subjects received a moderate intensity and 0.8% (12/1561) subjects received a low intensity statin at baseline. A total of 9.9% (156/1561) subjects were treated with ezetimibe.

A total of 22.0% (344/1561) of subjects were either partially or completely intolerant to statins. The most common symptoms of statin intolerance (partial or complete) were muscle ache (83.1%; 286/344), cramping (25.0%; 86/344), and other symptoms (21.5%; 74/344).

In study ORION-11, 96.8% (1565/1617) of subjects received LMT, 94.7% (1532/1617) of subjects received statin therapy and 11.8% (191/1617) received other LMT.

Based on the FDA feedback received on September 13, 2019, and in order to be consistent with ACC/AHA guidelines, simvastatin 40 mg was to be included in the moderate intensity stain group instead of the high intensity statin group as prespecified in the final SAP. Based on the SAP Addendum defined criteria in which simvastatin 40 mg is considered a moderate intensity statin, 78.0% (1261/1617) of subjects were on a high intensity statin at baseline. A total of 15.5% (251/1617) of subjects received a moderate intensity and 0.4% (6/1617) subjects received a low intensity statin at baseline. A total of 7.1% (114/1617) subjects were treated with ezetimibe.

A total of 11.4% (185/1617) of subjects were either partially or completely intolerant to statins. The most common symptoms of statin intolerance (partial or complete) were muscle ache (70.3%; 130/185), other symptoms (38.4%; 71/185), and cramping (8.6%; 16/185).

- ***Participant flow***

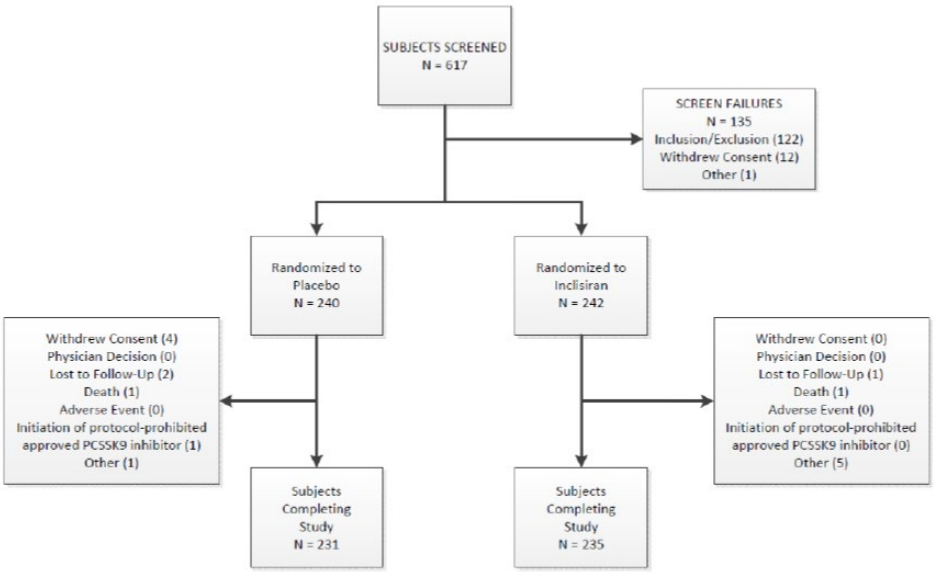
Subject disposition was summarised as follows:

- The number of subjects in each analysis population along with reasons for exclusion from each analysis population was summarised by treatment group for all randomised subjects.
- The number of subjects who completed the study or who discontinued early along with reasons for early discontinuation was summarised by treatment group for each analysis population.
- The duration on study (number of days from the first date of treatment to the date of last recorded contact / participation date in the database) was summarised by treatment for each analysis population.
- The number of subjects in each treatment group was summarised by country for each analysis population.

Completers were defined as subjects who completed the Day 540 visit. A summary of the number of subjects by visit was provided by treatment group for each analysis population.

The overall dispositions of subjects for the studies ORION-9, ORION-10, and ORION-11 are summarised in the figures below.

**Figure 3.3.5.1: Disposition of Subjects for Study ORION-9 – All Screened Subjects**

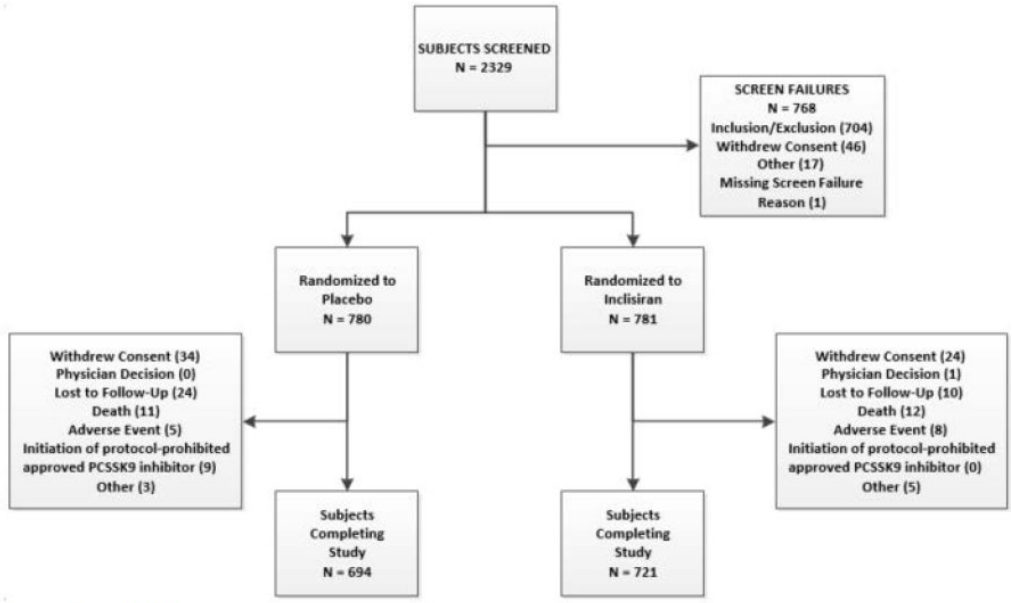



Source: Figure 14.1

A total of 3.8% (9/240) of placebo-treated subjects discontinued the study. The most common reasons for discontinuation from the study were withdrawal of consent (1.7%; 4/240) and lost to follow-up (0.8%; 2/240). There was 1 discontinuation from the study due to death and no placebo-treated subject discontinued due to AEs.

A total of 2.9% (7/242) of inclisiran-treated subjects discontinued the study. The most common reason for discontinuation from the study was other (2.1%; 5/242); other reasons included subject moved to a new house and screen failure (accidentally randomised). There was 1 discontinuation from the study due to death and no inclisiran-treated subject discontinued due to AEs.

**Figure 3.3.5.2: Disposition of Subjects for Study ORION-10 – All Screened Subjects**

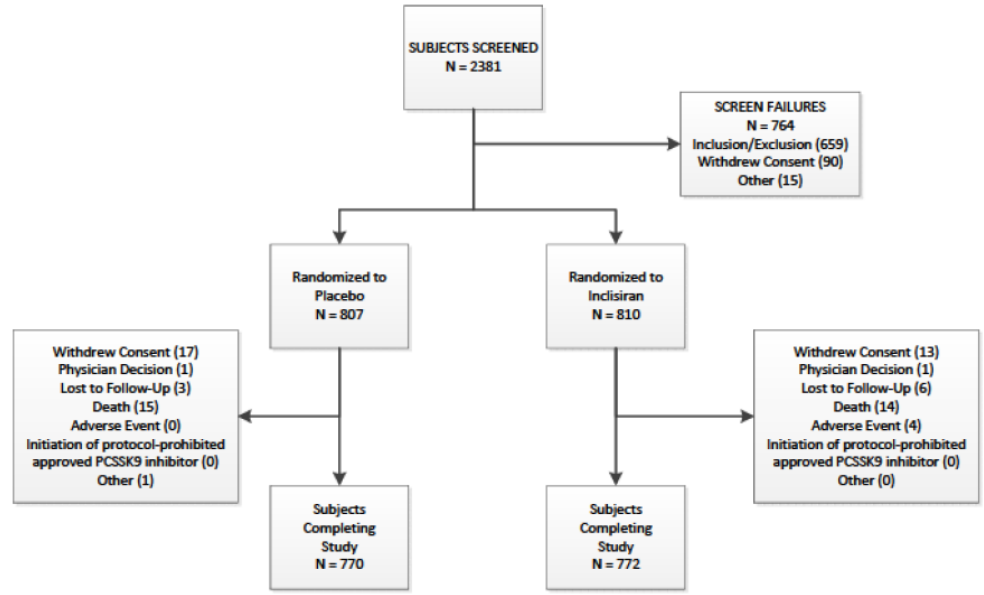



Source: Figure 14.1

A total of 11.0% (86/780) placebo-treated subjects discontinued the study. The most common reasons for discontinuation from the study was withdrawal of consent (4.4%; 34/780) followed by lost to follow-up (3.1%; 24/780). There were 1.4% (11/780) discontinuations from the study due to death and 0.6% (5/780) subjects discontinued from the study due to TEAEs.

A total of 7.7% (60/781) inclisiran-treated subjects discontinued the study. The most common reasons for discontinuation from the study were withdrawal of consent (3.1%; 24/781) followed by death (1.5%; 12/781). Eight (8) of 781 (1.0%) of subjects discontinued the study due to TEAEs.

**Figure 3.3.5.3: Disposition of Subjects for Study ORION-11 – All Screened Subjects**




Source: Figure 14.1

A total of 4.6% (37/807) placebo-treated subjects discontinued the study. The most common reasons for discontinuation from the study were withdrawal of consent (2.1%; 17/807) followed by death

(1.9%; 15/807). There were no discontinuations in placebo-treated subjects from the study due to AEs.

A total of 4.7% (38/810) inclisiran-treated subjects discontinued the study. The most common reasons for discontinuation from the study was death (1.7%; 14/810) and withdrawal of consent (1.6%; 13/810). There were 0.5% (4/810) discontinuations in inclisiran-treated subjects from the study due to AEs.

- ***Numbers analysed***

The primary efficacy analysis was based on the intent-to-treat (ITT) population defined as all subjects who were randomised into the study.

*Study ORION-9*

In study ORION-9 off the 482 randomised subjects 240 (100%) received IMP and 242 (100%) received placebo and were included in the ITT-Population.

*Study ORION-10*

In study ORION-10 off the 1561 randomised subjects 780 (100%) received IMP and 781 (100%) received placebo and were included in the ITT-Population.

*Study ORION-11*

In study ORION-11 off the 1617 randomised subjects 807 (100%) received IMP and 810 (100%) received placebo and were included in the ITT-Population

- ***Outcomes and estimation***

**Co-Primary endpoints**

An overview of the results of the co-primary endpoints of the 3 confirmatory studies is presented in the table below.

**Table 3.3.5.2: Primary Efficacy Endpoints from Phase III Studies**

| Co-primary endpoints | | ORION-9 (N=482 HeFH) | | | ORION-10 (N=1561 ASCVD) | | | ORION-11 (N=1617 ASCVD[1]) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Placebo | Inclisiran | Δ | Placebo | Inclisiran | Δ | Placebo | Inclisiran | Δ |
| **ITT population** | | 240 | 242 | | 780 | 781 | | 807 | 810 | |
| **Δ LDL-C At Day 510** | | | | | | | | | | |
| **Observed values** | | +8% | -41% | -50% | +1% | -56% | -58% | +4% | -49% | -54% |
| **Imputation** | Washout | +8% | -40% | -48% | +1% | -51% | -52% | +4% | -46% | -50% |
| | PMM | +8% | -40% | -48% | +1% | -53% | -54% | +4% | -48% | -52% |
| | MMRM | +8% | -41% | -49% | +1% | -56% | -57% | +4% | -49% | -53% |
| **Time adj. Δ LDL-C Day 90-540** | | | | | | | | | | |
| **Imputation** | PMM | +6% | -38% | -44% | +3% | -51% | -54% | +3% | -46% | -49% |
| | MMRM | +6% | -38% | -45% | +3% | -53% | -56% | +3% | -47% | -50% |

Source: ISE Table 14.2.15.1.1, Table 14.2.15.1.2, Table 14.2.2.1.1.1, and Table 14.2.2.1.1.2
[1] Includes ASCVD Risk Equivalents
Abbreviations: ASCVD=atherosclerotic cardiovascular disease; MMRM = mixed effects model repeated measures; PMM = predictive mean matching; Washout = includes the "Modified" Washout for ORION-11

## Key Secondary Efficacy Endpoints

Results of the key secondary endpoints of the 3 confirmatory studies were as follows.

*Absolute Change in LDL-C from Baseline to Day 510*

The placebo-adjusted absolute change from baseline to Day 510 in LDL-C levels was -68.9 mg/dL (p<0.0001) [ORION-9], -54.1 mg/dL (p<0.0001) [ORION-10], and -51.9 mg/dL (p<0.0001) [ORION-11], respectively.

*Time-adjusted Absolute Change in LDL-C from Baseline after Day 90 and up to Day 540*

Compared to placebo, the time-adjusted absolute change from baseline after Day 90 and up to Day 540 was -62.7 mg/dL (p<0.0001) [ORION-9], -53.3 mg/dL (p<0.0001) [ORION-10], and -48.9 mg/dL (p<0.0001) [ORION-11], respectively.

*Percentage Change in PCSK9 from Baseline to Day 510*

The placebo-adjusted percentage change in PCSK9 from baseline to Day 510 was -78.3% (p<0.0001) [ORION-9], -83.3% (p<0.0001) [ORION-10, and 79.3% (p<0.0001) [ORION-11], respectively.

*Percentage Change in Total Cholesterol from Baseline to Day 510*

The placebo-adjusted percentage change in TC from baseline to Day 510 was -31.8% (p<0.0001) [ORION-9], -33.1% (p<0.0001) [ORION-10], and -29.8% (p<0.0001) [ORION-11], respectively.

*Percentage Change in Apo-B from Baseline to Day 510*

The placebo-adjusted percentage change in Apo-B from baseline to Day 510 was -36.1% (p<0.0001) [ORION-9], -43.1% (p<0.0001) [ORION-10], and -38.9% (p<0.0001) [ORION-11], respectively.

*Percentage Change in Non-HDL-C from Baseline to Day 510*

The placebo-adjusted percentage change in non-HDL-C from baseline to Day 510 was -42.4% (p<0.0001) [ORION-9], 47.4% (p<0.0001) [ORION-10], and 43.3% (p<0.0001) [ORION-11], respectively.

Sensitivity analyses using MMRM yielded similar results and were statistically significant (p<0.0001) across the 3 studies. Furthermore, the results were similar regardless of the analysis population (ITT, FAS, mITT) used.

Other secondary endpoints in lipid parameters also showed significant placebo-adjusted reductions in the inclisiran treatment groups across all 3 phase III studies.

Explorative endpoints evaluating to the effect of inclisiran on MACE (composite of CV death, resuscitated cardiac arrest, non-fatal MI, ischemic 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%; 10/240) and inclisiran-treated subjects (4.1%; 10/241) in study ORION-9 and was 10.2% (79/778) in placebo-treated compared to 7.4% (58/781) in inclisiran-treated subjects in study ORION-10, and 10.3% (83/804) compared to 7.8% (63/811), respectively, in study ORION-11].

- ***Ancillary analyses***

Analyses of the co-primary endpoints in the 3 phase III studies were conducted using 2 additional efficacy analysis populations (FAS and mITT Population). Similar, statistically significant (p<0.0001), placebo-adjusted differences were observed for both co-primary endpoints regardless of analysis population used.

**Tipping point Analyses**

Tipping point analyses were performed to demonstrate the shift parameters for the value of LDL-C, which were needed to switch the result from statistically significant to not statistically significant. The analyses showed that a high shift parameter was needed to switch the primary endpoint result to not statistically significant across the 3 studies. The tipping point analyses support the robustness of the study results.

**Subgroup Analyses of Efficacy**

*Study ORION-9*

Subgroup analyses for efficacy were performed based on 21 categories using MMRM to account for missing data. Placebo-adjusted LDL-C reductions favouring inclisiran were similar across most subgroups for 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. A statistically significant interaction was observed for above and below the median and quartiles of baseline LDL-C and PCSK9 levels for both coprimary endpoints. In all subgroups, inclisiran lowered LDL-C more than placebo (p<0.05)

*Study ORION-10*

Subgroup analyses were performed based on 18 categories. Similar LDL-C reductions were observed for all subgroups analysed for both co-primary endpoints, 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. Similar and statistically significant (p<0.0001) LDL-C reductions in favour of the inclisiran-treated group were observed regardless of subgroup analysed for both co-primary endpoints.

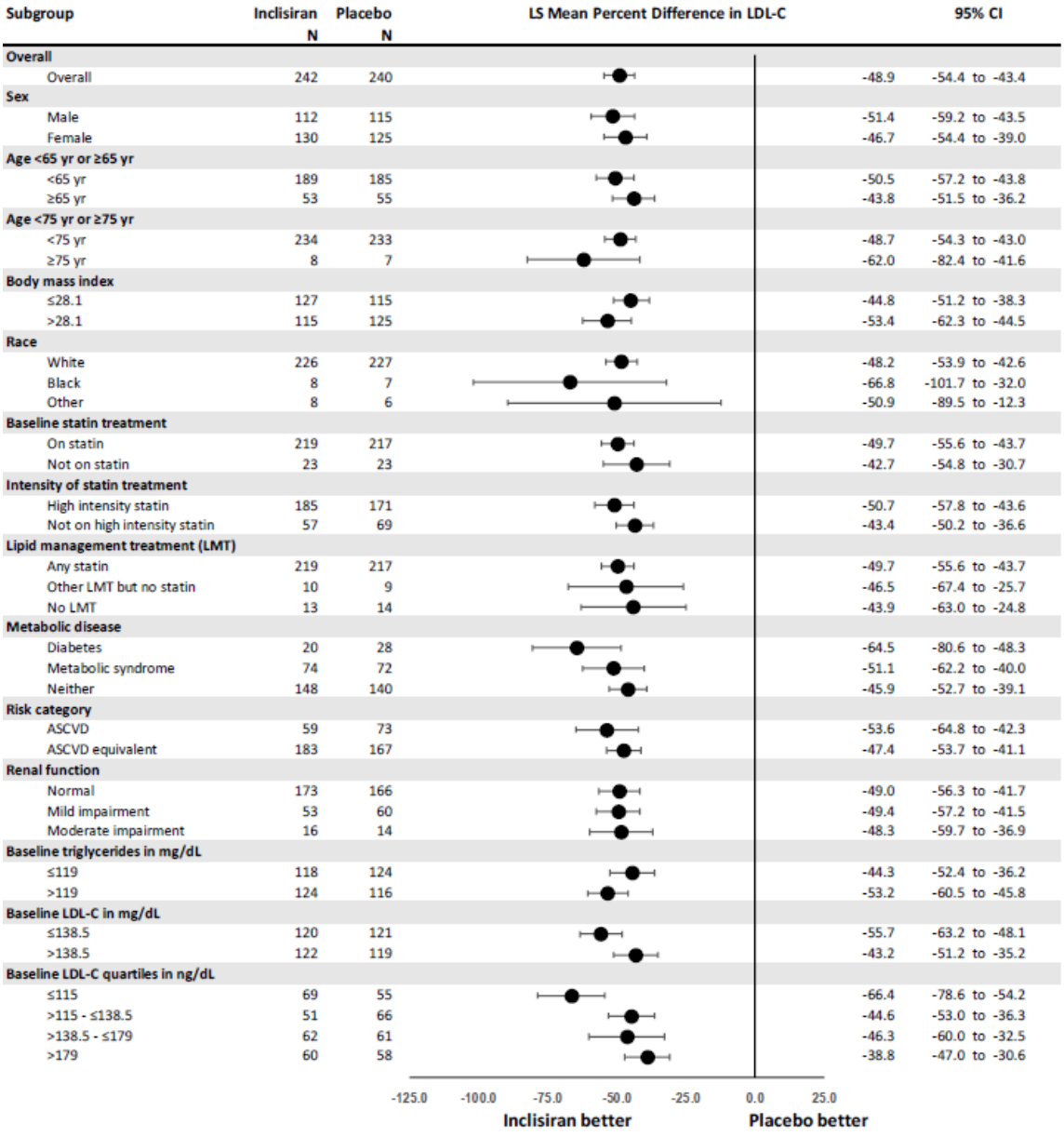
A greater placebo-adjusted percentage reduction in LDL-C was observed in subjects with below median baseline LDLR and below quartile baseline LDL, several of which are likely to have some inter-relationship.

A greater absolute LDL-C reduction was observed in subjects with below median baseline LDLR and below quartile baseline LDL.

*Study ORION-11*

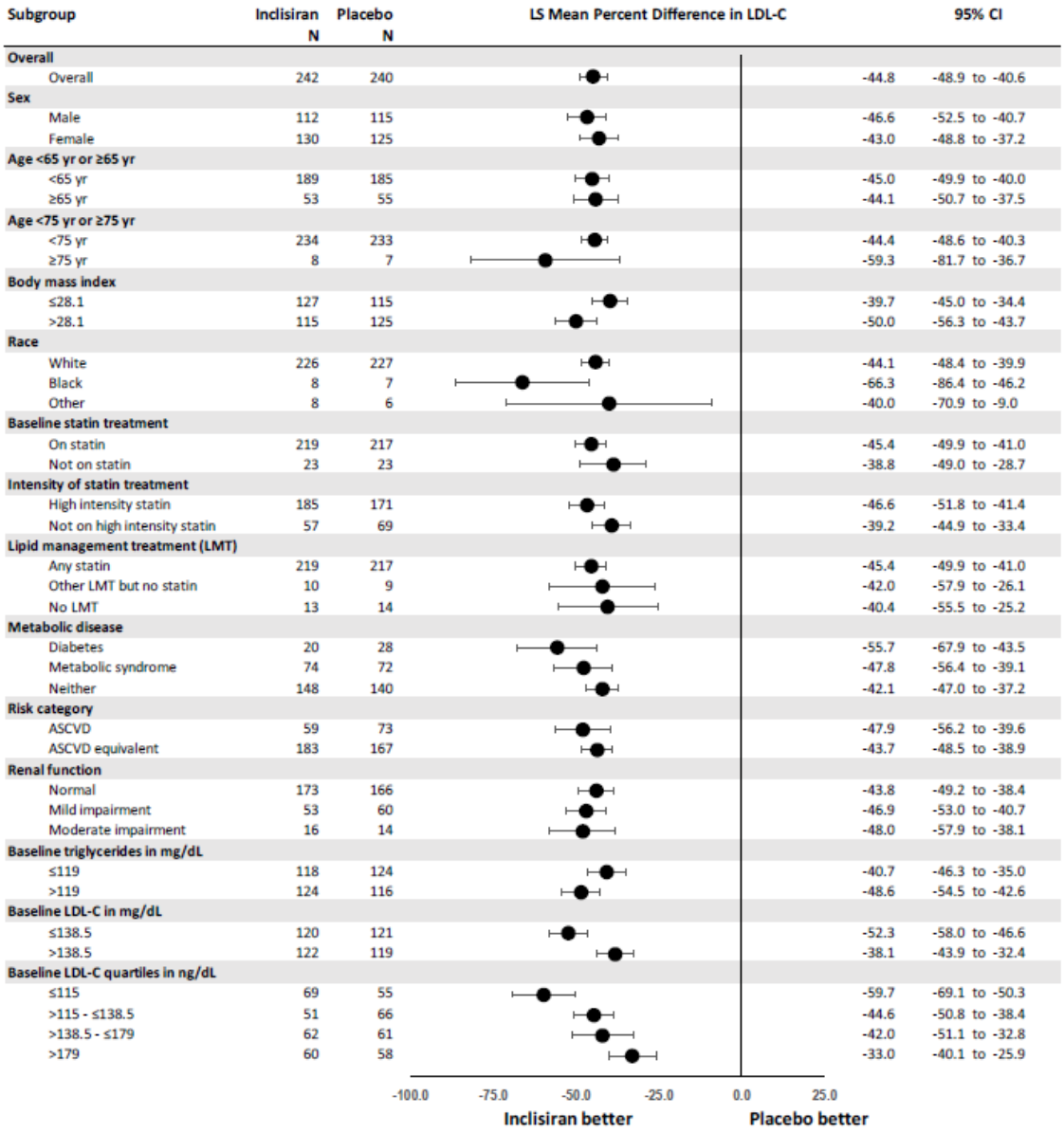
Subgroup analyses for efficacy were performed on 19 categories using MMRM to account for missing data. Placebo-adjusted LDL-C reductions favouring inclisiran were similar across most subgroups for percentage change in LDL-C from baseline to Day 510 and time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. A statistically significant interaction was observed for above and below the median and quartiles of baseline LDL-C and PCSK9 levels for both co-primary endpoints. In all subgroups, inclisiran lowered LDL-C more than placebo (p<0.05).

**Figure 3.3.5.4: Forest Plot of Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510 - Subgroup Analyses - ITT Population (Study ORION-9)**



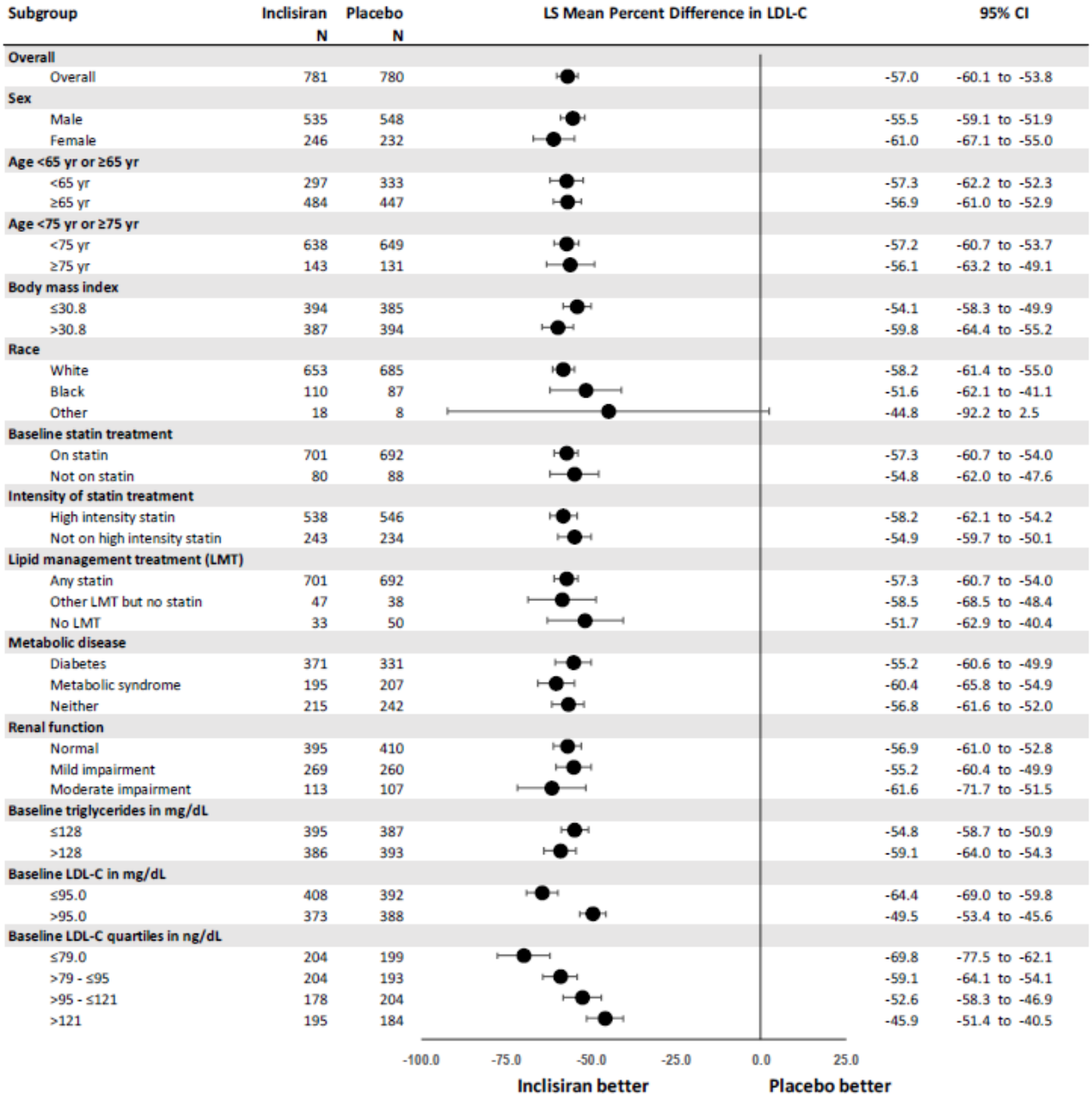

Source: Figure 14.2.14.1

**Figure 3.3.5.5: Forest Plot of Treatment Differences in Time-Adjusted LDL-C After Day 90 and Up to Day 540 - Subgroup Analyses (Study ORION-9)**




Source: Figure 14.2.14.2

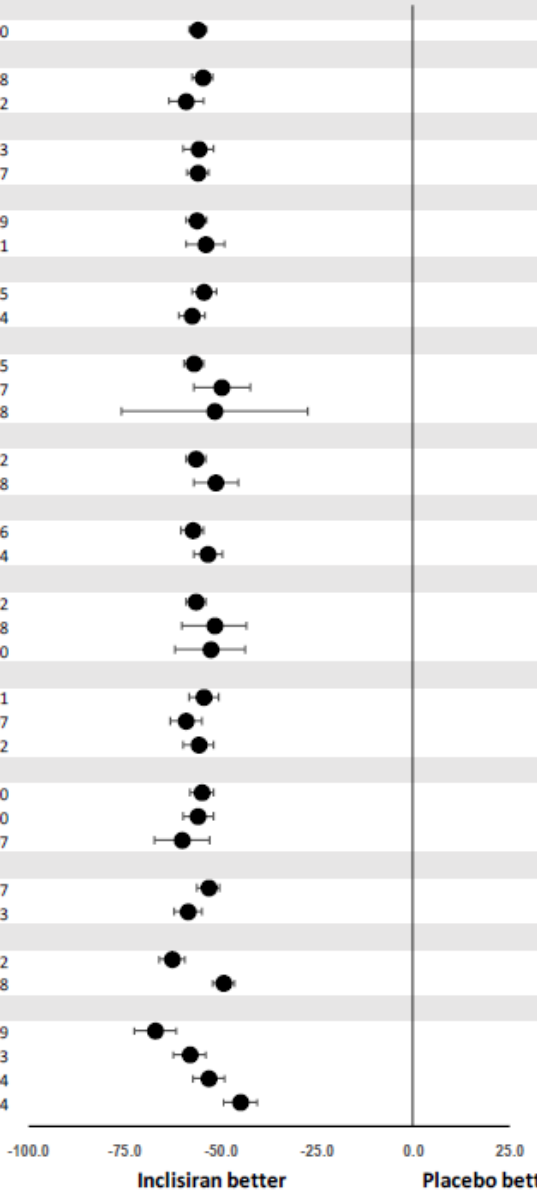
**Figure 3.3.5.6: Forest Plot of Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510 - Subgroup Analyses - ITT Population (Study ORION-10)**




Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

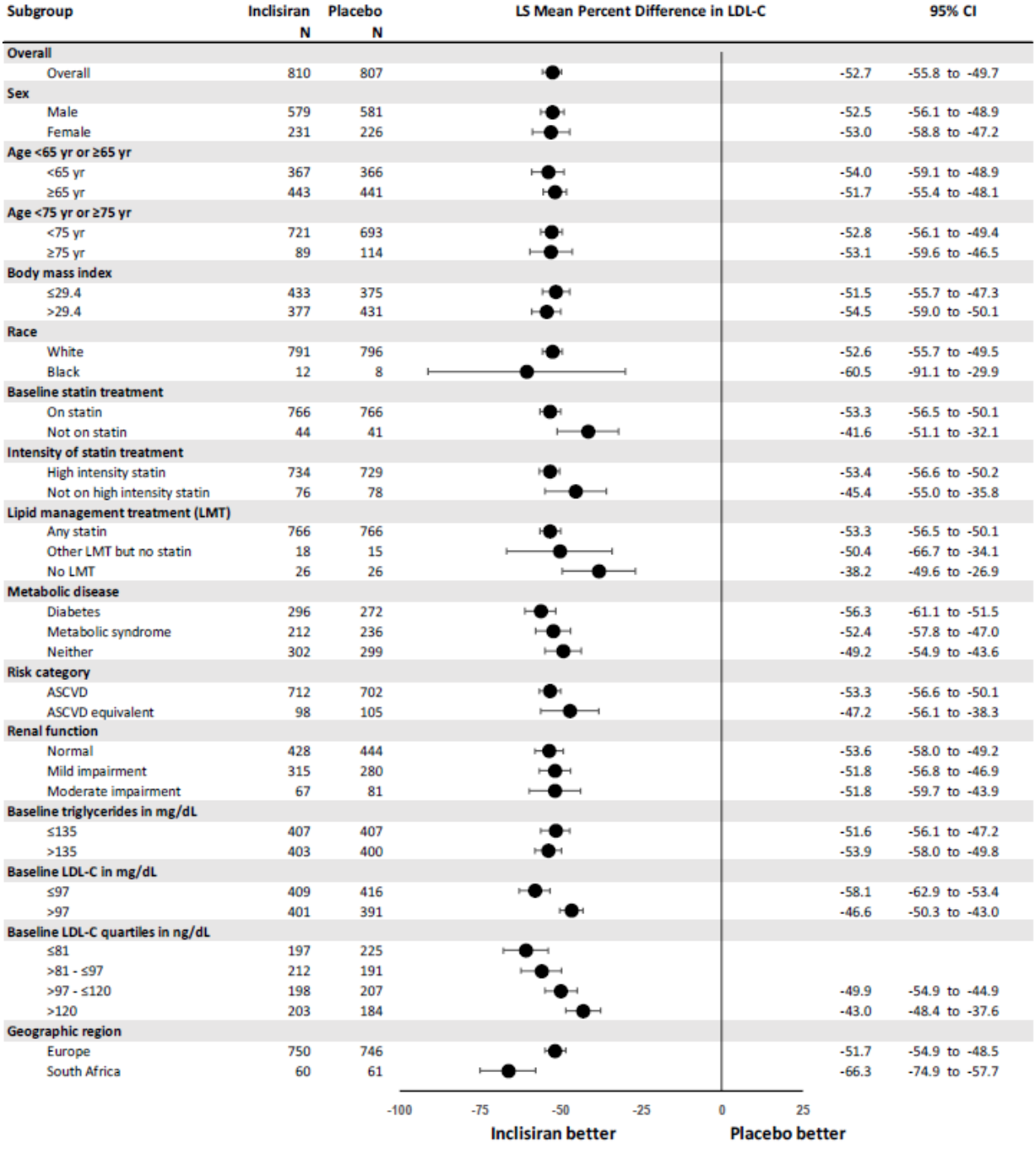
**Figure 3.3.5.7: Forest Plot of Treatment Differences in Time-Adjusted LDL-C After Day 90 and Up to Day 540 - Subgroup Analyses - ITT Population**

| Subgroup | Inclisiran N | Placebo N | LS Mean Percent Difference in LDL-C | 95% CI |
|---|---|---|---|---|
| **Overall** | | | | |
| Overall | 781 | 780 | -55.9 | -58.2 to -53.5 |
| **Sex** | | | | |
| Male | 535 | 548 | -54.7 | -57.4 to -52.0 |
| Female | 246 | 232 | -58.9 | -63.5 to -54.3 |
| **Age <65 yr or ≥65 yr** | | | | |
| <65 yr | 297 | 333 | -55.7 | -59.7 to -51.7 |
| ≥65 yr | 484 | 447 | -55.9 | -58.8 to -53.1 |
| **Age <75 yr or ≥75 yr** | | | | |
| <75 yr | 638 | 649 | -56.3 | -58.9 to -53.7 |
| ≥75 yr | 143 | 131 | -53.9 | -58.9 to -48.9 |
| **Body mass index** | | | | |
| ≤30.8 | 394 | 385 | -54.3 | -57.6 to -51.0 |
| >30.8 | 387 | 394 | -57.5 | -60.8 to -54.2 |
| **Race** | | | | |
| White | 653 | 685 | -57.0 | -59.5 to -54.5 |
| Black | 110 | 87 | -49.7 | -57.0 to -42.3 |
| Other | 18 | 8 | -51.5 | -75.7 to -27.3 |
| **Baseline statin treatment** | | | | |
| On statin | 701 | 692 | -56.5 | -59.0 to -54.0 |
| Not on statin | 80 | 88 | -51.2 | -57.0 to -45.3 |
| **Intensity of statin treatment** | | | | |
| High intensity statin | 538 | 546 | -57.3 | -60.2 to -54.4 |
| Not on high intensity statin | 243 | 234 | -53.3 | -57.0 to -49.5 |
| **Lipid management treatment (LMT)** | | | | |
| Any statin | 701 | 692 | -56.5 | -59.0 to -54.0 |
| Other LMT but no statin | 47 | 38 | -51.6 | -60.0 to -43.2 |
| No LMT | 33 | 50 | -52.7 | -61.8 to -43.6 |
| **Metabolic disease** | | | | |
| Diabetes | 371 | 331 | -54.5 | -58.3 to -50.6 |
| Metabolic syndrome | 195 | 207 | -59.1 | -63.2 to -54.9 |
| Neither | 215 | 242 | -55.8 | -59.7 to -51.8 |
| **Renal function** | | | | |
| Normal | 395 | 410 | -54.8 | -57.9 to -51.7 |
| Mild impairment | 269 | 260 | -55.9 | -59.9 to -51.9 |
| Moderate impairment | 113 | 107 | -60.0 | -67.3 to -52.8 |
| **Baseline triglycerides in mg/dL** | | | | |
| ≤128 | 395 | 387 | -53.2 | -56.2 to -50.2 |
| >128 | 386 | 393 | -58.5 | -62.1 to -54.9 |
| **Baseline LDL-C in mg/dL** | | | | |
| ≤95.0 | 408 | 392 | -62.6 | -66.0 to -59.2 |
| >95.0 | 373 | 388 | -49.2 | -52.2 to -46.3 |
| **Baseline LDL-C quartiles in ng/dL** | | | | |
| ≤79.0 | 204 | 199 | -67.0 | -72.3 to -61.6 |
| >79 - ≤95 | 204 | 193 | -58.1 | -62.3 to -54.0 |
| >95 - ≤121 | 178 | 204 | -53.1 | -57.2 to -49.0 |
| >121 | 195 | 184 | -44.9 | -49.2 to -40.6 |



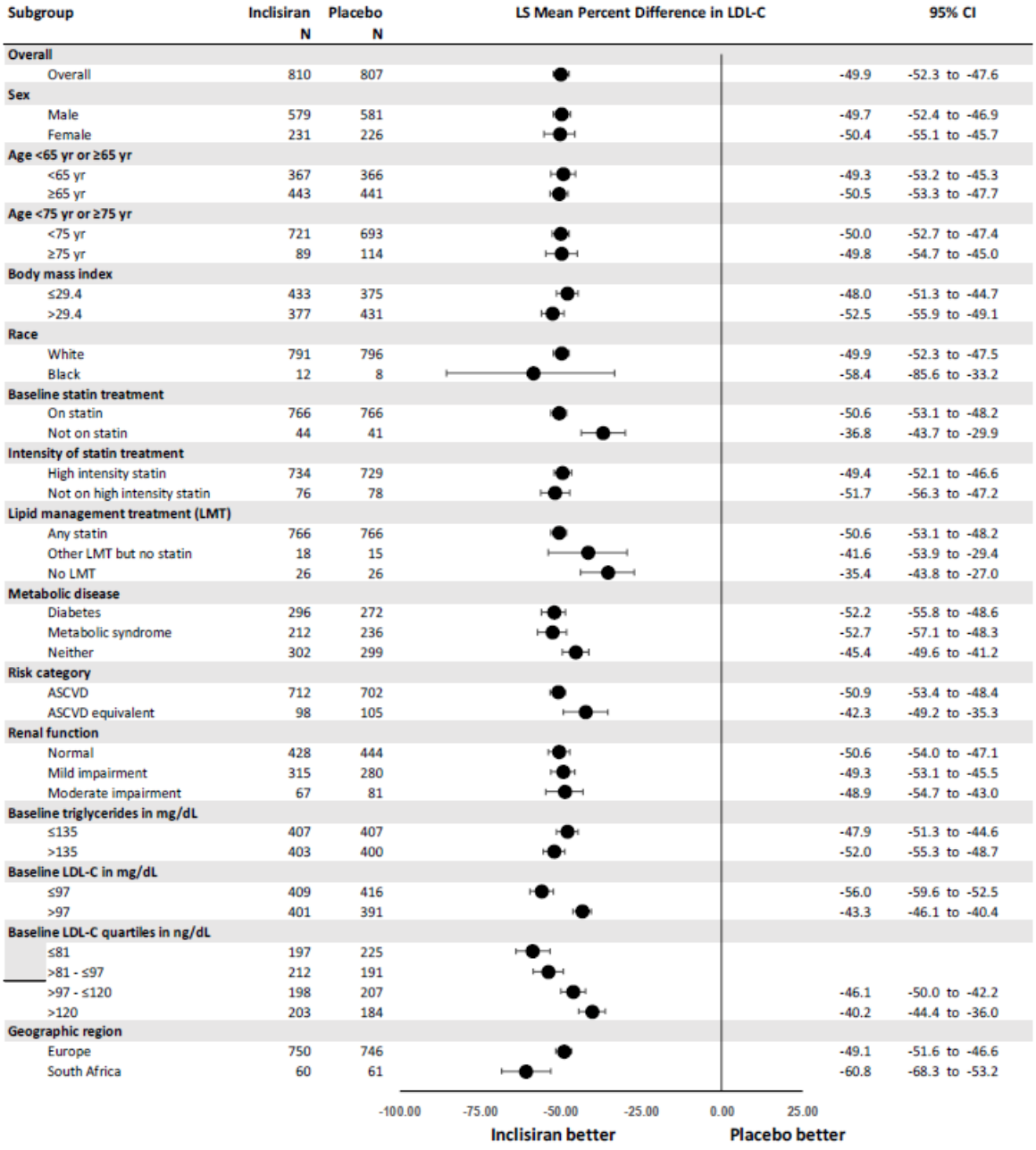

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

**Figure 3.3.5.8: Forest Plot of Treatment Difference in Percentage Change in LDL-C from Baseline to Day 510 – Subgroup Analyses - ITT Population (Study ORION-11)**




Source: Figure 14.2.14.1.

**Figure 3.3.5.9: Forest Plot of Treatment Differences in Time Adjusted Percentage Change in LDL-C After Day 90 and Up to Day 540 - Subgroup Analyses - ITT Population (Study ORION-11)**




Source: Figure 14.2.14.2

## Summary of main studies

The inclisiran clinical development programme included 3 phase III studies in 3 type of subjects, i.e. subjects with HeFH, subjects with ASCVD, and subjects with ASCVD-risk equivalents (type 2 diabetes, FH, and including subjects whose 10-year risk of a CV event assessed by Framingham Risk Score or equivalent has a target LDL-C of <100 mg/dL). The primary efficacy data are derived from all 3 confirmatory randomised, placebo-controlled studies in the proposed target population. Supportive efficacy data was obtained from the placebo-controlled phase II study ORION-1 conducted in subjects with high CV risk. All subjects in the efficacy studies had elevated LDL-C levels despite maximum tolerated dose of LDL-C lowering therapy.

Subjects who completed ORION-1 to at least Day 210 and whose LDL-C had returned to within 20% of the baseline value or who reached Day 360 (ORION-1) with no contraindication to receiving inclisiran or evolocumab had the option of participating in the open-label extension study ORION-3.

The following table summarises the efficacy results from the pivotal studies ORION-9, ORION-10, and ORION-11 supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment in later sections.

**Table 3.3.5.3: Summary of efficacy for trial ORION-9**

| **Title:** A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with heterozygous familial hypercholesterolemia (HeFH) and elevated low-density lipoprotein cholesterol (LDL-C). | | | |
|---|---|---|---|
| Study identifier | ORION-9 (MDCO-PCS-17-03) | | |
| Design | Randomised, multicentre, double-blind, placebo-controlled study. | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 540 Days<br>14 Days<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | inclisiran | | 300 mg inclisiran SC as single 1.5 mL injection on Day 1, Day 90, Day 270 and Day 450 (final Dose)<br>n = 242 |
| | placebo | | Placebo SC as single 1.5 ml injection on Day 1, Day 90, Day 270 and Day 450 (final dose)<br>n = 240 |
| Endpoints and definitions | Co-Primary endpoint | % change from baseline in LDL-C to Day 510 | Percentage change in LDL-C from Baseline to Day 510. |
| | Co-Primary endpoint | Time-adjusted % change in LDL-C from baseline after Day 90 up to Day 540 | This is the average percentage change in LDL-C from baseline after Day 90 and up to Day 540. This provides the average LDL-C between the dosing intervals |
| | Key secondary endpoint | absolute change in LDL-C from Baseline to Day 510 | Absolute change in LDL-C from Baseline to Day 510 |
| | Key secondary endpoint | Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 | Time-adjusted absolute change in LDL-C from Baseline after Day 90 and up to Day 540. |
| | Key secondary endpoint | % change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C. | Percentage change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C. |
| | Other secondary endpoint | Absolute change and percentage change in LDL-C | Absolute change and percentage change in LDL-C from Baseline to each assessment time up to Day 540. |
| | Other secondary endpoint | Absolute in PCSK9, TC, Apo-B and non-HDL-C. | Absolute change from Baseline to Day 510 in PCSK9, TC, Apo-B and non-HDL-C. |
| | Other | Individual | Individual responsiveness defined as the number of |

| | | | |
|---|---|---|---|
| | secondary endpoint | responsiveness | subjects reaching on-treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510. |
| | Other secondary endpoint | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from Baseline. |
| | Other secondary endpoint | | Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk. |
| | Other secondary endpoint | Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 | Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from Baseline at each subsequent visit to Day 540. |
| | Other secondary endpoint | Maximum percentage change in LDL-C | Maximum percentage change in LDL-C. This is calculated by finding the maximum individual LDL-C reduction at any post-baseline visit for each individual subject.<br>This value was used to compare against each subject's baseline value and use to calculate the percentage change from baseline to the lowest LDL-C value. |

| | |
|---|---|
| Database lock | Not provided |

**Results and Analysis**

| | | | |
|---|---|---|---|
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and timepoint description | Intent to treat in patients with HeFH and elevated LDL-C<br><br>540 Days | | |
| Effect estimate per arm | Treatment group | Inclisiran | Placebo |
| | Number of subject | 242 | 240 |
| | % change from baseline in LDL-C to Day 510 | -41.15 | 8.37 |
| | Time-adjusted Percentage Change from Baseline after Day 90 and up to Day 540 | -38.08 | 6.22 |
| Effect estimate per comparison | Primary endpoint | Comparison groups | Inclisiran vs. Placebo |
| | | % change from baseline vs placebo | -49.52 |
| | | 95% CI | -55.04,-43.99 |
| | | P-value | <0.0001 |
| | Co-Primary endpoint | Comparison groups | Inclisiran vs. Placebo |
| | | Time-adjusted Percentage Change | -44.30 |
| | | 95% CI | -48.48,-40.12 |
| | | P-value | <.0001 |
| Notes | | | |
| **Analysis description** | **Key Secondary analysis** | | |
| Analysis population | ITT-Population | | |
| Descriptive statistics and estimate variability | Treatment group | **Inclisiran** | **Placebo** |
| | Number of subject | 242 | 240 |
| | Absolute change in LDL-C from baseline to Day 510 | -58.95 | 9.94 |
| | | absolute change from baseline vs placebo | -68.89 |

| | | | |
|---|---|---|---|
| | | 95% CI | -77.11,-60.67 |
| | | p-value | <0.0001 |
| | Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 | -56.58 | 6.17 |
| | | absolute change from baseline vs placebo | -62.74 |
| | | 95% CI | -69.01,-56.48 |
| | | p-value | <0.0001 |
| | Percentage change in PCSK9 from baseline to Day 510 | -60.68 | 17.66 |
| | | %change from baseline | -78.34 |
| | | 95% CI | -83.65,-73.04 |
| | | p-value | <0.0001 |
| | Percentage change in TC from baseline to Day 510 | -25.11 | 6.66 |
| | | %change from baseline vs placebo | -31.77 |
| | | 95% CI | -35.59,-27.94 |
| | | p-value | <0.0001 |
| | Percentage change in Apo-B from baseline to Day 510 | | |
| | | -33.14 | 2.93 |
| | | %change from baseline vs placebo | -36.06 |
| | | 95% CI | -39.99,-32.14 |
| | | p-value | <0.0001 |
| | Percentage change in Non-HDL-C from baseline to Day 510 | -34.93 | 7.43 |
| | | %change from baseline vs placebo | -42.36 |
| | | 95% CI | -47.32,-37.40 |
| | | p-value | <0.0001 |
| **Analysis description** | **Other Secondary analysis** | | |
| Analysis population | ITT-Population | | |
| Descriptive statistics and estimate variability | Treatment group | **Inclisiran** | **Placebo** |
| | Number of subject | 242 | 240 |
| | Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540 | placebo-adjusted absolute change in LDL C from baseline at all timepoints | -53.4 mg/dL to -71.6 mg/dl |
| | | p-values | <0.0001 |
| | | placebo-adjusted percentage change in LDL-C from baseline at all timepoints | -39.1% to -50.5% |
| | | p-values | <0.0001 |
| | Absolute change in PCSK9 from baseline to Day 510 | -282.6 | 54.54 |
| | | absolute change from baseline vs placebo | -337.1 |
| | | 95% CI | -358.9,-315.3 |
| | | p-value | <0.0001 |
| | Absolute change in TC from baseline to Day 510 | -60.84 | 12.63 |
| | | absolute change from baseline vs placebo | -73.46 |
| | | 95% CI | -82.18,-64.74 |
| | | p-value | <0.0001 |
| | Absolute change in Apo-B from baseline to Day 510 | -42.48 | 1.86 |
| | | absolute change from baseline vs placebo | -44.33 |
| | | 95% CI | -49.27,-39.40 |
| | | p-value | <0.0001 |
| | Absolute change in Non-HDL-C from baseline to Day 510 | -64.31 | 10.30 |
| | | absolute change from baseline vs placebo | -74.61 |
| | | 95% CI | -83.31,-65.91 |
| | | p-value | <0.0001 |
| | Individual responsiveness defined as the number of subjects reaching on-treatment LDL-C Levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510 | <100 mg/dL<br>65.3% (158/242) | 8.8% (21/240) |
| | | | |
| | | <70 mg/dL<br>40.9% (99/242) | 1.3%; (3/240) |
| | | <50 mg/dL<br>19.0% (46/242) | 0.8% (2/240) |
| | | <25 mg/dL | |

| | | | |
|---|---|---|---|
| | | 0.8% (2/242) | 0.0% (0/240) |
| | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline at any time of the study | 66.0% (159/241) | 3.8% (9/239) |
| | Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk at Day 510 | LDL-C <70 mg/dl<br><br>52.5% (31/59) | <br><br>1.4% (1/71) |
| | | LDL-C <100 mg/dl<br><br>66.9% (115/172) | <br><br>8.9% (14/158) |
| **Analysis description** | **Exploratory description**<br>**Incidence of MACE (CV Death, Resuscitated Cardiac Arrest, Non-Fatal MI, and Stroke (Ischemic and Hemorrhagic))** | | |
| | Mace | 4.1% (10/241) | 4.2% (10/240) |
| | Total | 4.2% (20/481) | |
| | CV Death | 0.4% (1/241) | 0.0% (0/240) |
| | Total | 0.2% (1/481) | |
| | Non-Fatal MI | 3.7% (9/241) | 4.2% (10/240) |
| | Total | 4.0% (19/481) | |
| **Analysis description** | **Exploratory description**<br>**Proportion of Responders** | | |
| | Reduction in LDL-C at any time during study | 99.2% (239/241) | 81.2% (194/239) |

**Table 3.3.5.4: Summary of efficacy for trial ORION-10**

| | | | |
|---|---|---|---|
| **Title:** A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) elevated low-density lipoprotein cholesterol (LDL-C). | | | |
| Study identifier | ORION-10 (MDCO-PCS-17-04) | | |
| Design | Randomised, multicentre, double-blind, placebo-controlled study. | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 540 Days<br>14 Days<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | inclisiran | | 300 mg inclisiran SC as single 1.5 mL injection on Day 1, Day 90, Day 270 and Day 450 (final Dose)<br>n = 781 |
| | placebo | | Placebo SC as single 1.5 ml injection on Day 1, Day 90, Day 270 and Day 450 (final dose)<br>n = 780 |
| Endpoints and definitions | Co-Primary endpoint | % change from baseline in LDL-C to Day 510 | Percentage change in LDL-C from Baseline to Day 510. |
| | Co-Primary endpoint | Time-adjusted % change in LDL-C from baseline after Day 90 up to Day 540 | This is the average percentage change in LDL-C from baseline after Day 90 and up to Day 540. This provides the average LDL-C between the dosing intervals |
| | Key secondary endpoint | absolute change in LDL-C from Baseline to Day 510 | Absolute change in LDL-C from Baseline to Day 510 |
| | Key secondary endpoint | Time-adjusted absolute change in LDL- | Time-adjusted absolute change in LDL-C from Baseline after Day 90 and up to Day 540. |

| | | | |
|---|---|---|---|
| | | C from baseline after Day 90 and up to Day 540 | |
| | Key secondary endpoint | % change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C. | Percentage change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C. |
| | Other secondary endpoint | Absolute change and percentage change in LDL-C | Absolute change and percentage change in LDL-C from Baseline to each assessment time up to Day 540. |
| | Other secondary endpoint | Absolute in PCSK9, TC, Apo-B and non-HDL-C. | Absolute change from Baseline to Day 510 in PCSK9, TC, Apo-B and non-HDL-C. |
| | Other secondary endpoint | Individual responsiveness | Individual responsiveness defined as the number of subjects reaching on-treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510. |
| | Other secondary endpoint | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from Baseline. |
| | Other secondary endpoint | | Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk. |
| | Other secondary endpoint | Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 | Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from Baseline at each subsequent visit to Day 540. |
| | Other secondary endpoint | Maximum percentage change in LDL-C | Maximum percentage change in LDL-C. This is calculated by finding the maximum individual LDL-C reduction at any post-baseline visit for each individual subject.<br>This value was used to compare against each subject's baseline value and use to calculate the percentage change from baseline to the lowest LDL-C value. |
| Database lock | Not provided | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and timepoint description | Intent to treat in patients with atherosclerotic cardiovascular disease (ASCVD) and elevated low-density lipoprotein cholesterol (LDL-C)<br><br>540 Days | | |
| Descriptive statistics and estimate variability | Treatment group | **Inclisiran** | **Placebo** |
| | Number of subject | 781 | 780 |
| | % change from baseline in LDL-C to Day 510 | -56.34 | 1.30 |
| | Time-adjusted Percentage Change from Baseline after Day 90 and up to | -51.27 | 2.51 |

| | | | |
|---|---|---|---|
| | Day 540 | | |
| Effect estimate per comparison | Primary endpoint | Comparison groups | Inclisiran vs. Placebo |
| | | % change from baseline vs placebo | -57.64 |
| | | 95% CI | -60.86,-54.43 |
| | | P-value | <0.0001 |
| | Co-Primary endpoint | Comparison groups | Inclisiran vs. Placebo |
| | | Time-adjusted Percentage Change | -53.78 |
| | | 95% CI | -56.23,-51.33 |
| | | P-value | <.0001 |
| Notes | | | |

| **Analysis description** | **Key Secondary analysis** | | |
|---|---|---|---|
| Analysis population | ITT-Population | | |
| Descriptive statistics and estimate variability | Treatment group | **Inclisiran** | **Placebo** |
| | Number of subject | 781 | 780 |
| | Absolute change in LDL-C from baseline to Day 510 | -56.18 | -2.06 |
| | | absolute change from baseline vs placebo | -54.12 |
| | | 95% CI | -57.37,-50.88 |
| | | p-value | <0.0001 |
| | Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 | -53.66 | -0.39 |
| | | absolute change from baseline vs placebo | -53.28 |
| | | 95% CI | -55.75,-50.80 |
| | | p-value | <0.0001 |
| | Percentage change in PCSK9 from baseline to Day 510 | -69.78 | 13.52 |
| | | %change from baseline | -83.30 |
| | | 95% CI | -89.25,-77.34 |
| | | p-value | <0.0001 |
| | Percentage change in TC from baseline to Day 510 | -33.56 | -0.42 |
| | | %change from baseline vs placebo | -33.13 |
| | | 95% CI | -36.80,-32.69 |
| | | p-value | <0.0001 |
| | Percentage change in Apo-B from baseline to Day 510 | -44.81 | -1.72 |
| | | %change from baseline vs placebo | -43.09 |
| | | 95% CI | -45.50,-40.67 |
| | | p-value | <0.0001 |
| | Percentage change in Non-HDL-C from baseline to Day 510 | -47.41 | -0.05 |
| | | %change from baseline vs placebo | -47.36 |
| | | 95% CI | -50.25,-44.47 |
| | | p-value | <0.0001 |

| **Analysis description** | **Other Secondary analysis** | | |
|---|---|---|---|
| Analysis population | ITT-Population | | |
| Descriptive statistics and estimate variability | Treatment group | **Inclisiran** | **Placebo** |
| | Number of subject | 781 | 780 |
| | Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540 | placebo-adjusted absolute change in LDL C from baseline at all timepoints | -46.1mg/dL to -59.4mg/dL |
| | | p-values | <0.0001 |
| | | placebo-adjusted percentage change in LDL-C from baseline at all timepoints | -48.5% to -61.4% |
| | | p-values | <0.0001 |
| | Absolute change in PCSK9 from baseline to Day 510 | -316.1 | 17.87 |
| | | absolute change from baseline vs placebo | -333.9 |
| | | 95% CI | -351.1,-316.7 |
| | | p-value | <0.0001 |
| | Absolute change in TC from baseline to Day 510 | -64.76 | -3.20 |
| | | absolute change from baseline vs placebo | -61.55 |

| | | | |
|---|---|---|---|
| | | 95% CI | -65.35,-57.76 |
| | | p-value | <0.0001 |
| | Absolute change in Apo-B from baseline to Day 510 | -44.74 | -3.08 |
| | | absolute change from baseline vs placebo | -41.66 |
| | | 95% CI | -43.89,-39.44 |
| | | p-value | <0.0001 |
| | Absolute change in Non-HDL-C from baseline to Day 510 | -67.31 | -3.11 |
| | | absolute change from baseline vs placebo | -64.20 |
| | | 95% CI | -67.89,-60.50 |
| | | p-value | <0.0001 |
| | Individual responsiveness defined as the number of subjects reaching on-treatment LDL-C Levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510 | <100 mg/dL<br>83.4% (651/781) | 49.6% (387/780) |
| | | | |
| | | <70 mg/dL<br>74.4% (581/781) | 15.3%; (119/780) |
| | | <50 mg/dL<br>61.8% (483/781) | 2.4% (19/780) |
| | | <25 mg/dL<br>20.5% (160/781) | 0.5% (4/780) |
| | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline at any time of the study | 91.4% (701/767) | 6.5% (50/767) |
| | Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk at Day 510 | LDL-C <70 mg/dl<br><br>84.1% (581/691) | 17.9% (119/666) |
| **Analysis description** | **Exploratory description**<br>**Incidence of MACE (CV Death, Resuscitated Cardiac Arrest, Non-Fatal MI, and Stroke (Ischemic and Hemorrhagic))** | | |
| | Mace | 7.4% (58/781) | 10.2% (79/778) |
| | Total | 8.8% (137/1559) | |
| | CV Death | 0.9% (7/781) | 0.6% (5/778) |
| | Total | 0.8% (12/1559) | |
| | Resuscitated Cardiac Arrest | 0.1% (1/781) | 0.1% (1/778) |
| | Total | 0.1% (2/1559) | |
| | Non-Fatal MI | 5.1% (40/781) | 8.2% (64/778) |
| | Total | 6.7% (104/1559) | |
| | Stroke (Ischemic or Hemorrhagic) | 1.5% (12/781) | 1.3% (10/778) |
| | Total | 1.4% (22/1559) | |

**Table 3.3.5.5: Summary of efficacy for trial ORION-11**

| | | |
|---|---|---|
| **Title:** A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C). | | |
| Study identifier | ORION-11 (MDCO-PCS-17-08) | |
| Design | Randomised, multicentre, double-blind, placebo-controlled study. | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | 540 Days<br>14 Days<br>not applicable |
| Hypothesis | Superiority | |
| Treatments groups | inclisiran | 300 mg inclisiran SC as single 1.5 mL injection on Day 1, Day 90, Day 270 and Day 450 (final Dose)<br>n = 810 |
| | placebo | Placebo SC as single 1.5 ml injection on Day 1, Day |

| | | | |
|---|---|---|---|
| | | | 90, Day 270 and Day 450 (final dose)<br>n = 807 |
| Endpoints and definitions | Co-Primary endpoint | % change from baseline in LDL-C to Day 510 | Percentage change in LDL-C from Baseline to Day 510. |
| | Co-Primary endpoint | Time-adjusted % change in LDL-C from baseline after Day 90 up to Day 540 | This is the average percentage change in LDL-C from baseline after Day 90 and up to Day 540. This provides the average LDL-C between the dosing intervals |
| | Key secondary endpoint | absolute change in LDL-C from Baseline to Day 510 | Absolute change in LDL-C from Baseline to Day 510 |
| | Key secondary endpoint | Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 | Time-adjusted absolute change in LDL-C from Baseline after Day 90 and up to Day 540. |
| | Key secondary endpoint | % change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C. | Percentage change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C. |
| | Other secondary endpoint | Absolute change and percentage change in LDL-C | Absolute change and percentage change in LDL-C from Baseline to each assessment time up to Day 540. |
| | Other secondary endpoint | Absolute in PCSK9, TC, Apo-B and non-HDL-C. | Absolute change from Baseline to Day 510 in PCSK9, TC, Apo-B and non-HDL-C. |
| | Other secondary endpoint | Individual responsiveness | Individual responsiveness defined as the number of subjects reaching on-treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510. |
| | Other secondary endpoint | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from Baseline. |
| | Other secondary endpoint | | Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk. |
| | Other secondary endpoint | Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 | Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from Baseline at each subsequent visit to Day 540. |
| | Other secondary endpoint | Maximum percentage change in LDL-C | Maximum percentage change in LDL-C. This is calculated by finding the maximum individual LDL-C reduction at any post-baseline visit for each individual subject.<br>This value was used to compare against each subject's baseline value and use to calculate the percentage change from baseline to the lowest LDL-C value. |

| | | | |
|---|---|---|---|
| Database lock | 15 August 2019 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and timepoint description | Intent to treat in patients with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C)<br><br>540 Days | | |
| Descriptive statistics and estimate variability | Treatment group | **Inclisiran** | **Placebo** |
| | Number of subject | 810 | 807 |
| | % change from baseline in LDL-C to Day 510 | -49.30 | 4.20 |
| | Time-adjusted Percentage Change from Baseline after Day 90 and up to Day 540 | -46.58 | 3.35 |
| Effect estimate per comparison | Primary endpoint | Comparison groups | Inclisiran vs. Placebo |
| | | % change from baseline vs placebo | -53.50 |
| | | 95% CI | -56.66,-50.35 |
| | | P-value | <0.0001 |
| | Co-Primary endpoint | Comparison groups | Inclisiran vs. Placebo |
| | | Time-adjusted Percentage Change | -49.92 |
| | | 95% CI | -52.29,-47.55 |
| | | P-value | <.0001 |
| Notes | | | |
| **Analysis description** | **Key Secondary analysis** | | |
| Analysis population | ITT-Population | | |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Treatment group | **Inclisiran** | **Placebo** |
| | Number of subject | 810 | 807 |
| | Absolute change in LDL-C from baseline to Day 510 | -50.91 | 0.96 |
| | | absolute change from baseline vs placebo | -51.87 |
| | | 95% CI | -55.01,-48.72 |
| | | p-value | <0.0001 |
| | Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 | -48.63 | 0.31 |
| | | absolute change from baseline vs placebo | -48.94 |
| | | 95% CI | -51.39,-46.48 |
| | | p-value | <0.0001 |
| | Percentage change in PCSK9 from baseline to Day 510 | -63.64 | 15.62 |
| | | %change from baseline | -79.27 |
| | | 95% CI | -81.97,-76.57 |
| | | p-value | <0.0001 |
| | Percentage change in TC from baseline to Day 510 | -28.00 | 1.79 |
| | | %change from baseline vs placebo | -29.79 |
| | | 95% CI | -31.78,-27.81 |
| | | p-value | <0.0001 |
| | Percentage change in Apo-B from baseline to Day 510 | -38.15 | 0.79 |
| | | %change from baseline vs placebo | -38.94 |
| | | 95% CI | -41.21,-36.67 |
| | | p-value | <0.0001 |
| | Percentage change in Non-HDL-C from baseline to Day 510 | -41.16 | 2.15 |
| | | %change from baseline vs placebo | -43.32 |
| | | 95% CI | -46.04,-40.60 |
| | | p-value | <0.0001 |
| **Analysis description** | **Other Secondary analysis** | | |

| | | | |
|---|---|---|---|
| Analysis population | ITT-Population | | |
| Descriptive statistics and estimate variability | Treatment group | **Inclisiran** | **Placebo** |
| | Number of subject | 810 | 807 |
| | Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540 | placebo-adjusted absolute change in LDL C from baseline at all timepoints | -41.8 mg/dL to -54.5 mg/dL |
| | | p-values | <0.0001 |
| | | placebo-adjusted percentage change in LDL-C from baseline at all timepoints | -42.5% to -54.2% |
| | | p-values | <0.0001 |
| | Absolute change in PCSK9 from baseline to Day 510 | -245.10 | 40.71 |
| | | absolute change from baseline vs placebo | -285.80 |
| | | 95% CI | -294.0,-277.6 |
| | | p-value | <0.0001 |
| | Absolute change in TC from baseline to Day 510 | | |
| | | -54.90 | 0.31 |
| | | absolute change from baseline vs placebo | -55.21 |
| | | 95% CI | -58.86,-51.56 |
| | | p-value | <0.0001 |
| | Absolute change in Apo-B from baseline to Day 510 | -38.89 | -1.24 |
| | | absolute change from baseline vs placebo | -37.66 |
| | | 95% CI | -39.77,-35.54 |
| | | p-value | <0.0001 |
| | Absolute change in Non-HDL-C from baseline to Day 510 | -58.77 | -0.53 |
| | | absolute change from baseline vs placebo | -58.25 |
| | | 95% CI | -61.83,-54.66 |
| | | p-value | <0.0001 |
| | Individual responsiveness defined as the number of subjects reaching on-treatment LDL-C Levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510 | <100 mg/dL<br>81.6% (661/810) | 52.7% (425/807) |
| | | <70 mg/dL<br>69.6% (564/810) | 12.9%; (104/807) |
| | | <50 mg/dL<br>51.9% (420/810) | 2.4% (19/807) |
| | | <25 mg/dL<br>11.7% (95/810) | 0.1% (1/807) |
| | Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from baseline at any time of the study | 81.9% (658/803) | 5.9% (47/800) |
| | Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk at Day 510 | LDL-C <70 mg/dl<br><br>81.7% (522/639) | 16.0% (103/644) |
| | | LDL-C <100 mg/dl<br><br>77.6% (66/85) | 30.5% (29/95) |
| **Analysis description** | **Exploratory description**<br>**Incidence of MACE (CV Death, Resuscitated Cardiac Arrest, Non-Fatal MI, and Stroke (Ischemic and Hemorrhagic))** | | |
| | Mace | 7.8% (63/811) | 10.3% (83/804) |
| | Total | 9.0% (146/1615) | |
| | CV Death | 1.1% (9/811) | 1.1% (9/804) |
| | Total | 1.1% (18/1615) | |
| | Resuscitated Cardiac Arrest | 0.4% (3/811) | 0.0% (0/804) |
| | Total | 0.2% (3/1615) | |
| | Non-Fatal MI | 5.8% (47/811) | 8.5% (68/804) |
| | Total | 7.1% (115/1615) | |
| | Stroke (Ischemic or Hemorrhagic) | 0.5% (4/811) | 1.0% (8/804) |
| | | 0.7% (12/1615) | |

| | | | |
|---|---|---|---|
| | Total | | |

## Analysis performed across trials (pooled analyses and meta-analysis)

In addition to the results presented above, the following pooled data are available.

In total, 93.5% (3422/3660) of the participating subjects completed the 3 confirmatory phase III studies. Pooled analyses were performed for these studies as follows: Efficacy Pool 1 includes all 3 phase III trials, ORION-9, ORION-10, and ORION-11 and Efficacy Pool 2 includes only ORION-10 and ORION-11 since ORION-9 includes subjects with HeFH who have different demographics (e.g., younger age) and disease profiles.

**Efficacy pool 1** included 3660 subjects (482, 1561, and 1617 subjects in ORION-9, ORION-10, and ORION-11, respectively) in the ITT-Population. Overall, 93.5% (3422/3660) of subjects completed the phase III studies [92.8% (1695/1827) of placebo-treated subjects and 94.3% (1728/1833) of inclisiran-treated subjects]. The most common reasons for discontinuing the study were withdrawn consent [placebo 55 (3%), inclisiran 37 (2%)], death [placebo 27 (1.5%), inclisiran 27 (1.5%)], and lost to follow-up [placebo 29 ([1.6%), inclisiran 17 (0.9%)].

**Efficacy pool 2** included 3178 subjects (1561 and 1617 subjects in ORION-10 and ORION-11, respectively) in the ITT Population. As in pool 1, most of the placebo- [92.2% (1464/1587)] and inclisiran-treated subjects [93.8% (1493/1591)] completed the study. The most common reasons for discontinuing the study were withdrawn consent [placebo51 (3.2%), inclisiran 37 (2.3%)], death [placebo 26 (1.6%), inclisiran 26 (1.6%)], and lost to follow-up [placebo 27 (1.7%), inclisiran 16 (1.0%)].

Demographic characteristics were adequately balanced between groups in both efficacy pools. Racial and ethnic diversity in efficacy pool 1 was adequate to demonstrate efficacy in White [92.3% (3378/3660)], Black [6.3% (232/3660)], and Hispanic [6.4% (236/3660)] subjects. A similar racial and ethnic profile was observed in efficacy pool 2 while other racial and ethnic groups were under-represented. Median age in efficacy pool 1 was comparable to efficacy pool 2 (66 and 65 years of age, respectively) while efficacy pool 1 had a slightly higher proportion of females included compared to efficacy pool 2 (32.5% and 29.4%, respectively).

Despite aggressive lipid-lowering treatment, in studies ORION-10 and ORION-11, the baseline LDL-C in subjects with ASCVD was 105 mg/dL and in ORION-9 in subjects with HeFH 153 mg/dL. Comorbidities are well represented within both efficacy pool 1 and efficacy pool 2. Diabetes was reported in 36.0% (1318/3660) of subjects and almost all were type II diabetes mellitus [35.1% (1286/3660)]. The phase III trials also included a characteristic sample of subjects [72.3% (2,648/3660)] with renal impairment which was either mild [55.9% (2,046/3660)], moderate [15.9% (582/3660)], or severe [0.5% (20/3660)] as assessed by the central laboratory at screening for study eligibility using eGFR.

Both efficacy pool 1 and efficacy pool 2 were comprised of a population at high risk for CV events (subjects with ASCVD or ASCVD-risk equivalents, HeFH). Efficacy Pool 1 included subjects with ASCVD [84.9% (3107/3660)] and ASCVD-risk equivalents including HeFH [15.1% (553/3660)]. Efficacy Pool 2 included 93.6% (2975/3178) subjects with ASCVD and 6.4% (203/3178) subjects with ASCVD-risk equivalents. Hypertension was reported at baseline for 79.8% (2919/3660) of subjects in efficacy pool 1 and 85.5% (2716/3178) in efficacy pool 2.

Almost all subjects in efficacy pool 1 [94.0% (3441/3660)] and efficacy pool 2 [94.1% (2989/3178)] were on statins at study entry and high-intensity statins were prescribed to 73.8% (2701/3660) in

efficacy pool 1 and 73.8% (2345/3178) in efficacy pool 2. In efficacy pool 1 and efficacy pool 2, <10% of subjects had new LMT or changed LMT during the study.

With muscle ache as the most common symptom of statin intolerance there were 17.8% (651/3660) subjects with partial or complete statin intolerance in efficacy pool 1 and 16.6% (529/3178) subjects with partial or complete statin intolerance in efficacy pool 2. Less than 8% of subjects had complete statin intolerance in efficacy pool 1 and efficacy pool 2. Ezetimibe was used by 14.0% (513/3660) in efficacy pool 1 and by 8.2% (261/3178) in efficacy pool 2. Nine (9) placebo- and no inclisiran-treated subject started a PCSK9 monoclonal antibody during the phase III studies (exclusion criteria).

**Baseline Demographic Characteristics**

An overview of the baseline demographic characteristics is given in the table below.

**Table 3.3.5.6: Demographics in Efficacy Pool 1 and Efficacy Pool 2 (ITT Population)**

| Category | Stat | Efficacy Pool 1 | | Efficacy Pool 2 | |
|---|---|---|---|---|---|
| | | Placebo (N=1827) | Inclisiran (N=1833) | Placebo (N=1587) | Inclisiran (N=1591) |
| Age (yrs) | N | 1827 | 1833 | 1587 | 1591 |
| | Mean ± SD | 63.9±9.87 | 64.1±9.98 | 65.2±8.79 | 65.6±8.63 |
| | Median | 65.0 | 65.0 | 66.0 | 66.0 |
| | (Q1, Q3) | 58,71 | 59,71 | 59,71 | 60,71 |
| | (Min, Max) | 21,89 | 20,90 | 34,89 | 20,90 |
| Age Category | | | | | |
| 18-<65 | n (%) | 884 (48.4) | 853 (46.5) | 699 (44.0) | 664 (41.7) |
| >=65 | n (%) | 943 (51.6) | 980 (53.5) | 888 (56.0) | 927 (58.3) |
| 18-<75 | n (%) | 1575 (86.2) | 1593 (86.9) | 1342 (84.6) | 1359 (85.4) |
| >=75 | n (%) | 252 (13.8) | 240 (13.1) | 245 (15.4) | 232 (14.6) |
| Gender | | | | | |
| Male | n (%) | 1244 (68.1) | 1226 (66.9) | 1129 (71.1) | 1114 (70.0) |
| Female | n (%) | 583 (31.9) | 607 (33.1) | 458 (28.9) | 477 (30.0) |
| Is this female a woman of child-bearing potential* | | | | | |
| Yes | n/N (%) | 45 / 583 (7.7) | 39 / 607 (6.4) | 11 / 458 (2.4) | 13 / 477 (2.7) |
| No | n/N (%) | 538 / 583 (92.3) | 568 / 607 (93.6) | 447 / 458 (97.6) | 464 / 477 (97.3) |
| Current use of Statins or other Lipid-modifying therapies | | | | | |
| Yes | n (%) | 1720 (94.1) | 1721 (93.9) | 1495 (94.2) | 1494 (93.9) |
| No | n (%) | 107 (5.9) | 112 (6.1) | 92 (5.8) | 97 (6.1) |
| Weight (kg)** | N | 1825 | 1833 | 1585 | 1591 |
| | Mean ± SD | 89.7±20.02 | 88.3±18.37 | 90.5±20.15 | 89.0±18.25 |
| | Median | 88.0 | 87.0 | 88.0 | 87.0 |
| | (Q1, Q3) | 75,101 | 76,99 | 76,101 | 77,100 |
| | (Min, Max) | 31,192 | 41,187 | 31,192 | 46,187 |
| Height (cm)** | N | 1826 | 1833 | 1586 | 1591 |
| | Mean ± SD | 170.5±9.76 | 170.2±10.16 | 170.5±9.70 | 170.3±10.01 |
| | Median | 171.0 | 171.0 | 171.4 | 171.3 |
| | (Q1, Q3) | 164,178 | 163,178 | 164,177 | 163,178 |
| | (Min, Max) | 131,206 | 124,203 | 131,206 | 124,203 |
| BMI (kg/m)** | N | 1825 | 1833 | 1585 | 1591 |
| | Mean ± SD | 30.7±5.82 | 30.4±5.66 | 31.0±5.87 | 30.6±5.62 |
| | Median | 29.9 | 29.6 | 30.2 | 29.8 |
| | (Q1, Q3) | 27,34 | 27,33 | 27,34 | 27,34 |
| | (Min, Max) | 10,65 | 17,81 | 10,65 | 17,81 |
| Waist Circumference (cm)** | N | 1819 | 1831 | 1580 | 1590 |
| | Mean ± SD | 104.6±14.83 | 104.0±14.07 | 105.5±14.73 | 104.8±13.77 |
| | Median | 103.5 | 103.0 | 104.0 | 104.0 |
| | (Q1, Q3) | 95,113 | 95,112 | 96,114 | 96,113 |
| | (Min, Max) | 56,203 | 62,208 | 56,203 | 62,208 |
| Race | | | | | |
| American Indian or Alaska Native | n (%) | 4 (0.2) | 4 (0.2) | 4 (0.3) | 3 (0.2) |
| Asian | n (%) | 8 (0.4) | 22 (1.2) | 3 (0.2) | 15 (0.9) |
| Black or African American | n (%) | 102 (5.6) | 130 (7.1) | 95 (6.0) | 122 (7.7) |
| Native Hawaiian or Other Pacific Islander | n (%) | 5 (0.3) | 7 (0.4) | 4 (0.3) | 7 (0.4) |
| White | n (%) | 1708 (93.5) | 1670 (91.1) | 1481 (93.3) | 1444 (90.8) |
| Ethnicity | | | | | |
| Hispanic or Latino | n (%) | 116 (6.3) | 120 (6.5) | 108 (6.8) | 113 (7.1) |
| Not Hispanic or Latino | n (%) | 1711 (93.7) | 1713 (93.5) | 1479 (93.2) | 1478 (92.9) |
| Country | | | | | |
| Canada | n (%) | 11 (0.6) | 12 (0.7) | 0 (0.0) | 0 (0.0) |
| Czech Republic | n (%) | 16 (0.9) | 17 (0.9) | 11 (0.7) | 10 (0.6) |
| Germany | n (%) | 41 (2.2) | 42 (2.3) | 41 (2.6) | 42 (2.6) |
| Denmark | n (%) | 26 (1.4) | 23 (1.3) | 0 (0.0) | 0 (0.0) |
| Spain | n (%) | 42 (2.3) | 42 (2.3) | 0 (0.0) | 0 (0.0) |
| United Kingdom | n (%) | 231 (12.6) | 231 (12.6) | 231 (14.6) | 231 (14.5) |
| Hungary | n (%) | 52 (2.8) | 52 (2.8) | 52 (3.3) | 52 (3.3) |
| Netherlands | n (%) | 19 (1.0) | 19 (1.0) | 0 (0.0) | 0 (0.0) |
| Poland | n (%) | 357 (19.5) | 360 (19.6) | 357 (22.5) | 360 (22.6) |
| Sweden | n (%) | 16 (0.9) | 18 (1.0) | 0 (0.0) | 0 (0.0) |
| Ukraine | n (%) | 54 (3.0) | 55 (3.0) | 54 (3.4) | 55 (3.5) |
| United States | n (%) | 812 (44.4) | 814 (44.4) | 780 (49.1) | 781 (49.1) |
| South Africa | n (%) | 150 (8.2) | 148 (8.1) | 61 (3.8) | 60 (3.8) |

Source: Table 14.1.8.1.1 and Table 14.1.8.1.2

* This number is based on the number of females in the population.

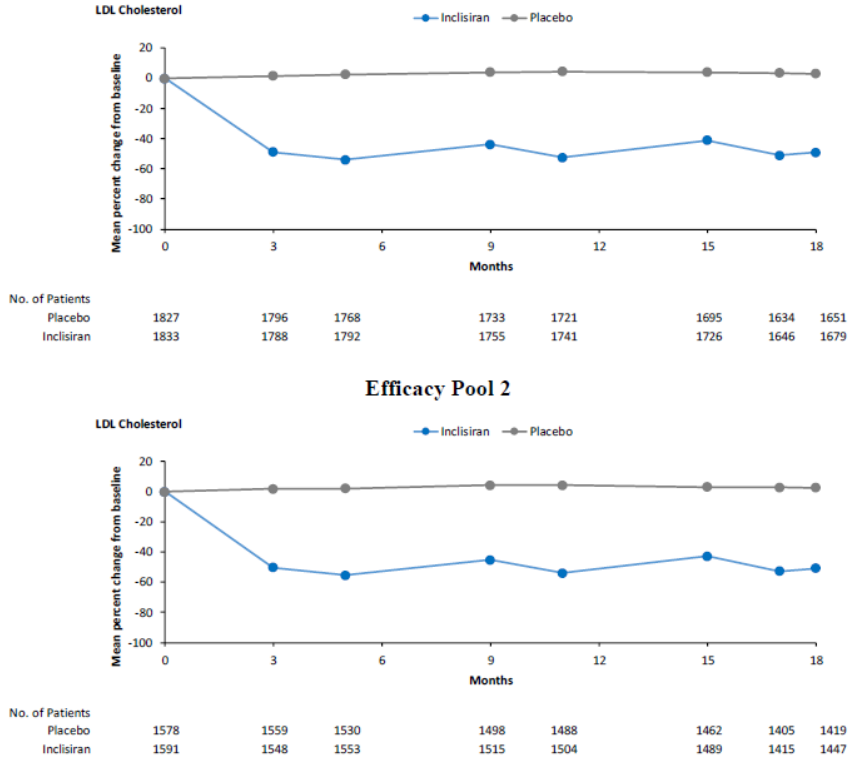
** This number is based on the number of subjects who answered the question on the CRF.

Abbreviations: BMI=body mass index; ITT=intent-to-treat; Max=maximum; Min=minimum; Q=quartile; SD=standard deviation

### Co-Primary Endpoints

Results of the co-primary efficacy endpoints showed that in the observed case placebo-adjusted LDL-C percentage change from baseline to Day 510 was -54.7% (95% CI -56.82,-52.61, p<0.0001) in efficacy pool 1 and -55.6% (95% CI -57.83,-53.31, p<0.0001) in efficacy pool 2. Using a washout model to account for missing data, the placebo-adjusted LDL-C percentage change from baseline to Day 510 was -50.7% (95% CI -52.86,-48.43, p<0.0001) in efficacy pool 1 and -51.0% (95% CI -53.40,-48.61, p<0.0001) in efficacy pool 2. The placebo-adjusted time-adjusted LDL-C percentage change from baseline after Day 90 and up to Day 540 was -50.5% (95% CI -52.11,-48.93, p<0.0001) in efficacy pool 1 and -51.4% (95% CI -53.15,-49.72, p<0.0001) in efficacy pool 2.

**Figure 3.3.5.11: Percentage Change from Baseline LDL-C (mg/dL) by Visit in Efficacy Pool 1 and Efficacy Pool 2-ITT Population**




Source: Figure 14.2.1.3.1 and Figure 14.2.1.3.2
Abbreviations: ITT=Intent-to-Treat; LDL-C=low-density lipoprotein cholesterol; SEM=standard error of the mean

### Key Secondary Endpoints

Results of the key secondary endpoints showed statistically significant placebo-adjusted absolute reductions in LDL-C from baseline to Day 510 of -55.1 (95% CI -57.36,-52.82, p<0.0001) in efficacy pool 1 and -52.9 (95% CI -55.22,-50.67, p<0.0001) in efficacy pool 2.

Placebo-adjusted time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 in efficacy pool 1 was -52.7 (95% CI -54.39,-50.91, p<0.0001) and in efficacy pool 2 was -51.0 (95% CI -52.79,-49.29, p<0.0001).

Treatment with inclisiran reduced PCSK9 levels from baseline to Day 510 by >75% consistently in all 3 phase III studies [efficacy pool1 -80.9 (95% CI -83.78,-78.02, p<0.0001) efficacy pool 2 -81.3 (95% CI -84.48,-78.02, p<0.0001)].

Inclisiran lowered TC (-31.49 efficacy pool 1, -31.44 efficacy pool 2), Apo-B (-40.3 efficacy pool 1, -41.0 efficacy pool 2), and non-HDL-C (-45.0 efficacy pool 1, -45.3 efficacy pool 2) with p-values <0.0001, respectively, compared with placebo, consistent with the changes in LDL-C resulting from PCSK9 inhibition and consistently across efficacy pool 1 and efficacy pool 2.

## Clinical studies in special populations

The subjects included in the 3 confirmatory studies were ≥18 years of age. No children or adolescents ≤18 years of age were recruited for the studies.

Results of the co-primary endpoints in the different age groups in the 3 studies are presented in the tables below.

**Table 3.3.5.7: Percent Change in LDL-C from Baseline to Day 540 and Time Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540 by Age in Study ORION-9 (ITT-Population)**

| | **Age 18 - <65** | | **Age ≥65 (Older subjects)** | | **Age ≥75 (Older subjects)** | |
|---|---|---|---|---|---|---|
| **Treatment** | **Inclisiran** | **Placebo** | **Inclisiran** | **Placebo** | **Inclisiran** | **Placebo** |
| **n/N** | 189/242 | 185/240 | 53/242 | 55/240 | 8/242 | 7/240 |
| %change in LDL-C from baseline to Day 510 | -38.05 | 10.92 | -45.46 | -0.88 | -57.03 | 6.23 |
| % change from baseline vs placebo | -48.96 | | -44.58 | | -63.26 | |
| 95% CI | -55.77,-42.16 | | -52.65,-36.52 | | NA | |
| P-value | <0.0001 | | <0.0001 | | NA | |
| Time adjusted %change in LDL-C from baseline after Day 90 and up to Day 540 | -36.70 | 7.79 | -43.00 | 0.91 | -54.48 | 4.78 |
| % change from baseline vs placebo | -44.49 | | -43.91 | | -59.26 | |
| 95% CI | -49.47,-39.50 | | -50.46,-37.37 | | NA | |
| p-value | <0.0001 | | <0.0001 | | NA | |

Abbr. NA = not available

**Table 3.3.5.8: Percent Change in LDL-C from Baseline to Day 540 and Time Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540 by Age in Study ORION-10 (ITT-Population)**

| | **Age 18 - <65** | | **Age ≥65 (Older subjects)** | | **Age ≥75 (Older subjects)** | |
|---|---|---|---|---|---|---|
| **Treatment** | **Inclisiran** | **Placebo** | **Inclisiran** | **Placebo** | **Inclisiran** | **Placebo** |
| **n/N** | 297/781 | 333/780 | 484/781 | 447/780 | 143/781 | 131/780 |
| %change in LDL-C from baseline to Day 510 | -52.06 | 0.45 | -50.80 | 1.32 | -48.68 | 1.71 |
| % change from baseline vs placebo | -52.51 | | -52.12 | | -50.39 | |
| 95% CI | -57.83,-47.20 | | -56.56,-47.68 | | -58.19,-42.60 | |
| P-value | <0.0001 | | <0.0001 | | <0.0001 | |
| Time adjusted %change in LDL-C from baseline after Day 90 and up to Day 540 | -50.65 | 2.96 | -51.62 | 2.16 | -49.67 | 1.56 |
| % change from baseline vs placebo | -53.61 | | -53.78 | | -51.23 | |
| 95% CI | -57.76,-49.46 | | -56.78,-50.79 | | -56.51,-45.95 | |
| p-value | <0.0001 | | <0.0001 | | <0.0001 | |

**Table 3.3.5.9: Percent Change in LDL-C from Baseline to Day 540 and Time Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540 by Age in Study ORION-11 (ITT-Population)**

| | **Age 18 - <65** | | **Age ≥65 (Older subjects)** | | **Age ≥75 (Older subjects)** | |
|---|---|---|---|---|---|---|
| **Treatment** | **Inclisiran** | **Placebo** | **Inclisiran** | **Placebo** | **Inclisiran** | **Placebo** |
| **n/N** | 367/810 | 366/807 | 443/810 | 441/807 | 89/810 | 114/807 |
| %change in LDL-C from baseline to Day 510 | -35.46 | 12.30 | -42.46 | 5.34 | -42.83 | 8.47 |
| % change from baseline vs placebo | -47.76 | | -47.80 | | -51.30 | |
| 95% CI | -53.23,-42.28 | | -51.85,-43.74 | | -58.59,-44.01 | |
| P-value | <0.0001 | | <0.0001 | | <0.0001 | |
| Time adjusted %change in LDL-C from baseline after Day 90 and up to Day 540 | -36.90 | 11.69 | -42.79 | 6.83 | -41.89 | 8.24 |
| % change from baseline vs placebo | -48.58 | | -49.62 | | -50.13 | |
| 95% CI | -52.51,-44.65 | | -52.52,-46.72 | | -55.06,-45.20 | |
| p-value | <0.0001 | | <0.0001 | | <0.0001 | |

### *Supportive study*

**ORION-2** (MDCO-PCS-16-02) was an open label, single arm, multicentre pilot study in subjects with homozygous familial hypercholesterolaemia (HoFH). The study was conducted in 3 countries in Europe, North America, and South Africa.

Four (4) subjects, males and females, ≥12 years of age with a diagnosis of HoFH by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration >500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of HeFH in both parents were enrolled and treated with inclisiran sodium 300 mg SC

The primary endpoint of the study was percentage change in LDL-C following 90 and 180 days of treatment.

The secondary endpoints of the study were absolute change and percentage change in LDL-C from Day 1 to each subsequent visit until Day 180 or final visit, absolute change and percentage change in PCSK9 from Day 1 to each subsequent visit until Day 180 or final visit, and absolute change and percentage change in TC, triglycerides, HDL-C, non-HDLC, VLDL-C, Apo-A1 Apo-B, and Lp(a) from Day 1 to each subsequent visit until Day 180 or final visit.

The treatment with inclisiran 300 mg SC injections resulted in a significant reduction in PCSK9 levels in all 4 subjects. 3 of the 4 subjects had also significant reductions in LDL-C levels while 1 subject did not show significant reduced LDL-C levels.

The mean percentage LDL-C reduction from baseline was 12.3% and 21.0% at Day 90 and Day 180, respectively. The maximum reductions in LDL-C were at Day 120 for two subjects and at Day 150 for a third subject. Based on this, the greatest reduction in LDL-C seemed to occur after the second dose of inclisiran.

The mean percentage PCSK9 reduction from baseline was 59.0% and 62.9% at Day 90 and Day 180, respectively. Decreases in other lipids, lipoproteins, and apolipoproteins were commensurate with the decreases in LDL-C.

Overall, the treatment with inclisiran in the specified population showed a consistently significant reduction in PCSK9 and a varying reduction in LDL-C.

For the preliminary results of the long-term efficacy in the ongoing open-label study ORION-3 see above.

Study reports from the long-term studies ORION-4, ORION-5, and ORION-8 have not been included in the dossier.

## 2.5.3. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

*LDL-C elevation despite maximum tolerated statins or statin intolerance*

Many patients with ASCVD treated with statins do not achieve their target LDL-C levels as recommended by learned societies[3]. Inclisiran, a siRNA was developed to inhibit the production of

[3] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019; 393: 407-415.

PCSK9, an enzyme that removes LDLRs on the surface of the liver cells and as a consequence leads to a reduction of LDL-C, a causal and modifiable factor in ASCVD.

The applicant performed 3 phase III studies to investigate and confirm the LDL-C lipid lowering treatment effect of inclisiran in maximum statin-treated and statin-intolerant patients. Patients with high CV risk eligible for further lipid lowering therapy based on their LDL-C level were included.

Inclusion criteria for the ORION-9 study are appropriate to specifically identify a HeFH population, while the inclusion criteria for studies ORION-10 and -11 reflect a population with increased CV risk and increased LDL-C levels, eligible for lipid lowering drug intervention in line with the ESC/EAS guideline recommendations. An elevated LDL-C level despite maximum statin therapy or statin intolerance was common to all subjects.

The 3 confirmatory studies are characterised by an almost identical double-blind, placebo-controlled, randomised (1:1), parallel-group design, which should allow for an adequate evaluation of the inclisiran treatment effect on LDL-C reduction. The time period covered by the co-primary endpoints of 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 to estimate the integrated effect on LDL-C over time is sufficiently long to establish the maximum stable LDL-C treatment effect. The secondary endpoints selected to corroborate effects by demonstrating the time profile for LDL-C reduction, effects on other potentially atherogenic lipoproteins, and on plasma PCSK9 levels are supportive for the primary endpoint and are acceptable.

Subjects should be on a stable lipid-lowering therapy ≥30 days prior to screening to stabilise lipid medication which is acceptable. To establish baseline LDL-C levels in phase III studies based on Day 1 (Visit 1) is appropriate.

Subjects eligible for lipid-lowering therapy were selected based on LDL-C level and CV risk classification. Serum LDL-C levels had to be ≥2.6 mmol/L (≥100 mg/dL) at screening in the HeFH population (study ORION-9), ≥1.8 mmol/L (≥70 mg/dL) in the ASCVD population (studies ORION-10 and -11), and ≥2.6 mmol/L (≥100 mg/dL) for ASCVD-risk equivalent subjects at screening (study ORION-11).

Subjects on statins should have been receiving a maximally tolerated dose. Maximum tolerated dose was defined as the maximum dose of statin that could be taken on a regular basis without intolerable AEs. Intolerance to any dose of any statin must have been documented as historical AEs attributed to the statin in question. Definition of statin intolerance was rigorously defined as documented evidence of intolerance to all doses of at least 2 different statins.

The exclusion criteria are generally acceptable to optimise study adherence and reduce potential dropouts, reduce potential tolerability issues with background medication, and exclude any possible relevant confounding.

## *Efficacy data and additional analyses*

*Phase II studies*

The phase II programme includes the dose finding study ORION-1 and its long-term extension study ORION-3 to evaluate the transition from evolocumab, a PCSK9-antibody, to inclisiran and study ORION-2 in subjects with HoFH.

**ORION-1** was a placebo-controlled, double-blind, randomised trial in subjects with high CV risk and elevated LDL-C, while ORION-3 was an open label, long term extension study in subjects with ASCVD or ASCVD-risk equivalents and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapy who have completed study ORION-1. ORION-2 was an open label, single arm, multicentre pilot study in subjects with HoFH. The ongoing study ORION-5 will present more data of inclisiran efficacy in subjects with HoFH and elevated LDL-C.

In the single dose groups, the response showed a dose dependency between single doses of 200 mg and 300 mg, with no additional effect at a single dose of 500 mg. The maximum mean LDL-C reduction of 58.9 mg/dL (50.9%) was observed at Day 60 following administration of a single dose of 300 mg inclisiran on Day 1. The LS mean LDL-C reduction was 27.9%, 38.4%, and 41.9% following a single dose of 200 mg, 300 mg, and 500 mg inclisiran, respectively, compared to a 2.1% increase in the placebo group (all $p<0.0001$).

In the double dose groups, the response showed dose dependency across the dose range studied (double doses of 100 mg, 200 mg, and 300 mg). The highest dose of 300 mg administered on Day 1 and Day 90 resulted in a maximum mean LDL-C reduction of 67.7 mg/dL (55.5%) at Day 150. The LS mean LDL-C reduction was 35.5%, 44.9%, and 52.6% following two doses of 100 mg, 200 mg, and 300 mg inclisiran, respectively, compared to a 1.8% increase in the placebo group (all $p<0.0001$). As expected, the responses were greater in the double inclisiran dose groups compared to the single inclisiran dose groups with an additional reduction from a second dose of inclisiran at Day 90 beyond that achieved at Day 60. The greatest reduction in LDL-C levels at Day 180 (52.6%) was observed in association with the 300 mg dose of inclisiran administered on Day 1 followed by a second dose on Day 90.

**ORION-3** is an ongoing long-term extension open-label study for subjects who completed ORION-1; subjects who received inclisiran in ORION-1 are receiving inclisiran throughout ORION-3 and will be referred to as the inclisiran only group. Subjects who received placebo in ORION-1 received evolocumab for 1 year and were then transitioned to inclisiran for the remainder of the study; this group is referred to as the switching group.

As of 8 May 2019 (data cut-off date), at Day 210 in study ORION-3 change from baseline LDL-C (calculated) was -50.6% ($p<0.0001$) in the inclisiran only group. The mean percentage change in LDL-C from ORION-1 baseline in the inclisiran only group at Day 30 was -51.4% and the response to inclisiran after each 6-monthly dose was consistent. There was no attenuation of effect as similar responses (over 50% reduction in LDL-C) were seen 30 days after each subsequent dose out to Day 570. Similarly, mean LDL-C levels were consistently changed by at least -63.5 mg/dL 30 days after each dose out to Day 570.

Following the first dose in ORION-3, the mean percentage change in PCSK9 from ORION-1 baseline at Day 30 was -72.2%. Response to inclisiran after each 6-monthly dose was consistent. Similar responses (percentage change of at least -74.8% in PCSK9) were observed 30 days after each subsequent dose out to Day 570. Similarly, changes in mean absolute PCSK9 levels were consistently at least -311.8 µg/L 30 days after each dose out to Day 570.

**ORION-2** was an open-label, single-arm, multicentre pilot study in subjects with HoFH. Males and females, ≥12 years of age with a diagnosis of HoFH by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration >500 mg/dL (13 mmol/L) together with either xanthoma before 10 years of age or evidence of HeFH in both parents were included in the study.

Inclisiran treatment resulted in robust and durable reductions in PCSK9 levels in all 4 subjects treated at a dose of 300 mg. Three (3) of the 4 subjects also had significantly reduced levels of LDL-C. One (1) subject had a significant reduction in PCSK9 but not a concomitant reduction in LDL-C. The mean

percentage LDL-C reduction from baseline was 12.3% and 21.0% at Day 90 and Day 180, respectively. The maximum reductions in LDL-C were at Day 120 for 2 subjects and at Day 150 for a third subject. Therefore, the second dose achieved a greater reduction in LDL-C than a single dose.

The mean percentage PCSK9 reduction from baseline was 59.0% and 62.9% at Day 90 and Day 180, respectively. Decreases in other lipids, lipoproteins, and apo-lipoproteins were according to the decreases in LDL-C.

*Phase III studies*

The primary efficacy data obtained in the proposed target population were derived from the 3 pivotal phase III studies, study ORION-9 in subjects with HeFH, ORION-10 in subjects with ASCVD, and ORION-11 in subjects with ASCVD or ASCVD-risk equivalents.

The 3 phase III studies demonstrate a significant and consistent lipid lowering effect with more than 50% reduction in LDL-C levels at day 510 compared to placebo in an international population with HeFH (ORION-9), an U.S. population with stable ASCVD and elevated LDL-C levels (110mg/dL on average) despite maximally tolerated statin therapy (ORION-10), and an international population with ASCVD or ASCVD-risk equivalents (ORION-11).

For the co-primary endpoints inclisiran treatment demonstrated in study ORION-9 a placebo-adjusted LDL-C change from baseline to Day 510 of -49.5% ($p<0.0001$) and from baseline after Day 90 and up to Day 540 of -44.3% ($p<0.0001$) with 99.2% (239/241) responders to inclisiran treatment. Furthermore, inclisiran treatment also lowered the lipid parameters (specified as key secondary endpoints) PCSK9 (-78.3%, $p<0.0001$), TC (-31.8%, $p<0.0001$), Apo-B (-36.1% $p<0.0001$), and non-HDL-C (-42.4%, $p<0.0001$), respectively.

Of the 482 participants in study ORION-9, 432 were tested of genetic variants. Of these, 256 (80.8%) had single LDLR causative variants, of whom 231 (90.2%) had LDLR pathogenic variants, 17 (6.6%) had probably pathogenic variants, and 8 (3.1%) had variants that were of uncertain significance. The mean between-group difference in the percent change in LDL cholesterol levels in subjects with two identified variants was -41.2%. The corresponding between-group difference among the subjects in whom a variant could not be identified was -59.2%. In the 50 subjects who did not undergo genetic testing, the corresponding between-group difference was -46.8%.

In study ORION-10, inclisiran treatment demonstrated a placebo-adjusted LDL-C change from baseline to Day 510 of -57.6% ($p<0.0001$) and from baseline after Day 90 and up to Day 540 of -53.8% ($p<0.0001$) for the co-primary endpoints, with 99.6% (762/765) responders to inclisiran treatment. Furthermore inclisiran treatment also lowered the lipid parameters (specified as key secondary endpoints) PCSK9 (-83.3%, $p<0.0001$), TC (-33.1%, $p<0.0001$), Apo-B (-43.1% $p<0.0001$), and non-HDL-C (-47.4%, $p<0.0001$).

For the co-primary endpoints in study ORION-11, inclisiran treatment demonstrated a placebo-adjusted LDL-C change from baseline to Day 510 of -53.5% ($p<0.0001$) and from baseline after Day 90 and up to Day 540 of -49.2% ($p<0.0001$) with 99.4% (797/802) responders to inclisiran treatment. Furthermore, inclisiran treatment also lowered the lipid parameters (specified as key secondary endpoints) PCSK9 (-79.3%, $p<0.0001$), TC (-29.8%, $p<0.0001$), Apo-B (-38.9% $p<0.0001$), and non-HDL-C (-43.3%, $p<0.0001$).

The reductions in LDL-C were seen in the majority of subjects taking high-intensity statins along with ezetimibe.

In the pooled data (482, 1561, and 1617 subjects from ORION-9, ORION-10, and ORION-11 included in efficacy pool 1; 1561 and 1617 subjects from ORION-10 and ORION-11 included in efficacy pool 2)

similar results were observed across the 2 pools. The LDL-C change from baseline to Day 510 (60 days after the last dose) was -54.7% in efficacy pool 1 and -55.6% in efficacy pool 2 and was long lasting (>50% on average for 6 months).

The proportion of high-intensity statin use was 73.8% (2701/3660) in efficacy pool 1 and 73.8% (2345/3178) in efficacy pool 2 which demonstrate the high efficacy of inclisiran in those subjects with a high CV risk taking high intensity lipid modifying drugs. The time-adjusted average LDL-C change from baseline within the dosing interval was -50.5% in efficacy pool 1 and -51.4% in efficacy pool 2. The LDL-C reduction could theoretically be accompanied by a 25% risk reduction for CV events after a treatment of 3 years or longer.

Reductions in other relevant lipid parameters (e.g., Apo-B, non-HDL-C, TC, Lp(a)) was consistent with the observed LDL-C reduction across the 2 pools.

For the age subgroups, data demonstrate that a robust mean reduction from baseline were observed with inclisiran for all primary and key secondary efficacy endpoints analysed in the subgroup of subjects 65–74 years, 75–84 years and 85+ years which was consistent with those seen in the overall population. Even that there was only a small number of elderly 85+ years, it could be demonstrated that inclisiran was just as effective as in the other groups observed in reducing the lipid parameters. Across the phase III studies inclisiran 300 mg SC injection on Day 1, Day 90, and every 6 months thereafter resulted in 50 to 58% lowering of LDL-C relative to placebo at Day 510 and a time-averaged 44 to 54% lowering of LDL-C after Day 90 through Day 540. Other lipid parameter like Apo-B were reduced by approximately 40%.

In all 3 studies sensitivity analyses using imputation for missing values produced similar results.

Moreover, results of the phase I studies demonstrated the effectiveness of inclisiran in subjects with renal and hepatic impairment.

The 3 ongoing long-term studies, including one dedicated study to evaluate the efficacy of inclisiran on CV outcomes, will reveal the impact of inclisiran on CV and overall mortality.

### 2.5.4. Conclusions on the clinical efficacy

Inclisiran demonstrated a long lasting and robust effect on PCSK9 reduction with a consequent reduction of LDL-C levels during 18 months of therapy. Most of the participants completed the efficacy studies with only few discontinuations. A strong positive effect could be observed on all primary and secondary clinical endpoints. More data on long-term efficacy and safety will be derived from the ongoing long-term studies.

The participants which were studied in the phase III programme adequately represent the target population for inclisiran as an adjunct to background lipid-lowering therapy in subjects who require further LDL-C lowering.

## *2.6. Clinical safety*

### *Patient exposure*

Patient exposure in the pivotal trials is extensive. Overall, safety from 4332 subjects have been provided, 2452 on inclisiran at any dose and 2118 on inclisiran at the recommended 300 mg dose;

safety data of more than 1500 subjects in the intended population given the proposed dose for at least 18 months have been included. Safety of inclisiran for more than 18 months of treatment is currently under evaluation in the 3 ongoing studies ORION-3, ORION-8, and ORION-4.

The phase III studies Safety Pool includes 3655 subjects, 1833 on inclisiran, and 1822 on placebo. Of these, 94% (3422/3655) completed the phase III studies, 94.4% (1731/1833) on inclisiran and 92.8% (1691/1822) on placebo; 90.6% (1650/1822) of placebo and 90.9% (1666/1833) of inclisiran-treated subjects received all 4 doses of study drug. There was no difference in mean subject-days of follow-up, 523 days in the placebo and 526 days in the inclisiran group.

In addition, the applicant has presented safety data from phase I and II studies individually, including trials in subjects with renal impairment and with hepatic impairment, a thorough QT study, and a pilot study in HoFH. The disposition of subjects included in the Safety Pool (phase III safety data) are given in the table below.

**Table 3.3.8.1: Disposition for the Safety Pool (phase III data)**

| Category | Placebo (N=1822) | Inclisiran (N=1833) |
|---|---|---|
| Completers* | 1691 (92.8) | 1731 (94.4) |
| Discontinued | 131 (7.2) | 102 (5.6) |
| | | |
| Withdrew Consent | 55 (3.0) | 36 (2.0) |
| Physician Decision | 0 (0.0) | 2 (0.1) |
| Lost To Follow-Up | 29 (1.6) | 17 (0.9) |
| Death | 27 (1.5) | 27 (1.5) |
| Adverse Event | 5 (0.3) | 12 (0.7) |
| PCSK9 Initiation** | 10 (0.5) | 0 (0.0) |
| Other | 5 (0.3) | 8 (0.4) |
| Missing Reason | 0 (0.0) | 0 (0.0) |

Source: Table 14.1.2.4
* A completer is defined as completing the Day 540 visit.
** PCSK9 Initiation = Initiation of protocol-prohibited approved PCSK9 inhibitor.
Abbreviation: PCSK9= proprotein convertase subtilisin/kexin type 9

Demographic characteristics as well as relevant CV risk factors, other comorbidities, lipid-modifying therapy (LMT) usage, and concomitant medications taken at randomisation were sufficiently balanced between treatment groups in the Safety Pool. LMT usage in the Safety Pool is detailed in the following table.

**Table 3.3.8.2: Day 1 Lipid-Modifying Therapy Usage in the Safety Pool**

| Category | Placebo (N=1822) | Inclisiran (N=1833) |
|---|---|---|
| No lipid-modifying therapy (LMT) at day 1 | 89 (4.9) | 72 (3.9) |
| Lipid-modifying therapy (LMT) at day 1 | 1733 (95.1) | 1761 (96.1) |
| | | |
| Statins | 1671 (91.7) | 1686 (92.0) |
| High Intensity | 1341 (73.6) | 1356 (74.0) |
| Moderate Intensity | 308 (16.9) | 305 (16.6) |
| Low Intensity | 13 (0.7) | 14 (0.8) |
| | | |
| Statins Only | 1249 (68.6) | 1298 (70.8) |
| | | |
| Other LMT | 484 (26.6) | 463 (25.3) |
| | | |
| Other LMT Only | 62 (3.4) | 75 (4.1) |

Source: Table 14.1.16.2.4

## *Adverse events*

Overall, in the phase III trials the incidence and type of common AEs was comparable between the placebo and the inclisiran group. In the Safety Pool, 77.3% (1409/1822) placebo and 78.0% (1430/1833) inclisiran-treated subjects had ≥1 treatment-emergent adverse event (TEAE). Treatment-emergent serious adverse events (TESAEs) occurred in 23.0% (419/1822) on placebo and 20.4% (374/1833) on inclisiran.

The most common AEs occurring more frequently on inclisiran than placebo were diabetes mellitus, nasopharyngitis, arthralgia, back pain, urinary tract infection, diarrhoea, bronchitis, cough, headache, angina pectoris, dizziness, pain in extremity, dyspnoea, and injection site reaction, while osteoarthritis, blood CPK increase, non-cardiac chest pain, and influenza occurred more frequently on placebo than inclisiran. However, except for injection site AEs [placebo 1.8% (33/1822); inclisiran 8.2% (150/1833)] these differences between groups were small. According to the data provided, injection site AEs were localised, predominantly mild or occasionally moderate, transient, and resolved without sequelae; no subject on inclisiran had a severe or serious injection site AE.

The incidence of severe AEs was higher on placebo than inclisiran [15.3% (278/1822) versus 13.0% (238/1833)]. The most common severe AEs were acute MI [1.5% (27/1822); 0.8% (14/1833)], coronary artery disease [0.9% (16/1822); 1.0% (18/1833)], and cardiac failure congestive [0.6% (11/1822); 0.4% (7/1833)].

**Table 3.3.8.3: Common (≥3% in either Group) TEAEs in the Safety Pool**

| | Placebo (N=1822) | | Inclisiran (N=1833) | | |
|---|---|---|---|---|---|
| Preferred Term | n (%) | E | n (%) | E | Risk Ratio* (95% CI) |
| Subject with at least one TEAE** | 1409 (77.3) | 5832 | 1430 (78.0) | 6115 | 1.0 (0.9, 1.0) |
| Diabetes mellitus | 207 (11.4) | 219 | 212 (11.6) | 230 | 1.0 (0.9, 1.2) |
| Nasopharyngitis | 134 (7.4) | 158 | 140 (7.6) | 164 | 1.0 (0.8, 1.3) |
| Upper respiratory tract infection | 103 (5.7) | 123 | 105 (5.7) | 119 | 1.0 (0.8, 1.3) |
| Hypertension | 104 (5.7) | 110 | 104 (5.7) | 112 | 1.0 (0.8, 1.3) |
| Arthralgia | 72 (4.0) | 81 | 91 (5.0) | 107 | 1.3 (0.9, 1.7) |
| Back pain | 77 (4.2) | 82 | 83 (4.5) | 92 | 1.1 (0.8, 1.5) |
| Urinary tract infection | 66 (3.6) | 81 | 81 (4.4) | 100 | 1.2 (0.9, 1.7) |
| Diarrhoea | 63 (3.5) | 69 | 71 (3.9) | 76 | 1.1 (0.8, 1.6) |
| Bronchitis | 50 (2.7) | 62 | 78 (4.3) | 88 | 1.6 (1.1, 2.2) |
| Cough | 54 (3.0) | 59 | 61 (3.3) | 67 | 1.1 (0.8, 1.6) |
| Headache | 56 (3.1) | 61 | 59 (3.2) | 83 | 1.0 (0.7, 1.5) |
| Angina pectoris | 57 (3.1) | 67 | 58 (3.2) | 73 | 1.0 (0.7, 1.4) |
| Dizziness | 55 (3.0) | 60 | 59 (3.2) | 63 | 1.1 (0.7, 1.5) |
| Osteoarthritis | 62 (3.4) | 68 | 49 (2.7) | 54 | 0.8 (0.5, 1.1) |
| Pain in extremity | 47 (2.6) | 54 | 60 (3.3) | 66 | 1.3 (0.9, 1.8) |
| Dyspnoea | 47 (2.6) | 50 | 59 (3.2) | 62 | 1.2 (0.9, 1.8) |
| Blood creatine phosphokinase increased | 61 (3.3) | 66 | 43 (2.3) | 44 | 0.7 (0.5, 1.0) |
| Non-cardiac chest pain | 58 (3.2) | 61 | 44 (2.4) | 46 | 0.8 (0.5, 1.1) |
| Influenza | 54 (3.0) | 59 | 41 (2.2) | 43 | 0.8 (0.5, 1.1) |
| Injection site reaction | 2 (0.1) | 2 | 56 (3.1) | 84 | 27.8 (6.8, 113.9) |

Source: ISS Table 14.3.1.3.2
* Risk Ratio of Inclisiran/Placebo
** Includes all subjects, not just subjects with most common AEs.
Note: Includes AEs with onset after study treatment began. Preferred terms are sorted by the total count first, then inclisiran, then placebo.
Abbreviations: CI=confidence interval; E=Event Count; TEAE=treatment-emergent adverse event

The incidence of TEAEs assessed by the investigators as having a reasonable possibility of being related to treatment was 9.7% (177/1822) in the placebo and 15.6% (286/1833) in the inclisiran group; the difference was primarily due to TEAEs at the injection site. On placebo, the most common

TEAEs considered related to study drug were CPK increased (0.7%; 13/1822), myalgia (0.6%; 11/1822), and fatigue (0.5%; 9/1822), while on inclisiran, these were injection site reaction (2.9%; 53/1833), injection site pain (2.0%; 37/1833), and injection site erythema (1.5%; 27/1833).

With the limited data available, AEs associated with renal or hepatic safety appear to be balanced between placebo and inclisiran groups.

No significant differences in neurological events and neurocognitive disorders between placebo and inclisiran were observed and ophthalmological AEs were balanced between groups.

**Table 3.3.8.4: Treatment-Emergent Adverse Events Related to Renal Events in the Safety Pool**

| | Placebo (N=1822) | | Inclisiran (N=1833) | | Total (N=3655) | |
|---|---|---|---|---|---|---|
| **Preferred Term** | **n (%)** | **E** | **n (%)** | **E** | **n (%)** | **E** |
| Number of subjects with at least one TEAE | 60 ( 3.3) | 64 | 60 ( 3.3) | 72 | 120 ( 3.3) | 136 |
| Acute kidney injury | 17 ( 0.9) | 17 | 19 ( 1.0) | 21 | 36 ( 1.0) | 38 |
| Blood creatinine abnormal | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Blood creatinine increased | 5 ( 0.3) | 5 | 7 ( 0.4) | 8 | 12 ( 0.3) | 13 |
| Blood urea increased | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Glomerular filtration rate abnormal | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 | 2 ( 0.1) | 2 |
| Glomerular filtration rate decreased | 10 ( 0.5) | 10 | 9 ( 0.5) | 9 | 19 ( 0.5) | 19 |
| Nephropathy toxic | 2 ( 0.1) | 2 | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 |
| Protein urine present | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Proteinuria | 3 ( 0.2) | 3 | 4 ( 0.2) | 4 | 7 ( 0.2) | 7 |
| Renal failure | 7 ( 0.4) | 7 | 4 ( 0.2) | 4 | 11 ( 0.3) | 11 |
| Renal impairment | 16 ( 0.9) | 17 | 23 ( 1.3) | 23 | 39 ( 1.1) | 40 |

Source: ISS Table 14.3.2.2
Note: See Appendix 5 of the ISAP for details on the search terms used. Preferred terms are sorted by the total count first, then inclisiran, then placebo.
Abbreviations: E=Event Count; ISAP= Integrated Statistical Analysis Plan; TEAE=treatment-emergent adverse event

**Table 3.3.8.5: Treatment-Emergent Adverse Events Related to Hepatic Events in the Safety Pool**

| | Placebo (N=1822) | | Inclisiran (N=1833) | | Total (N=3655) | |
|---|---|---|---|---|---|---|
| **Preferred Term** | **n (%)** | **E** | **n (%)** | **E** | **n (%)** | **E** |
| Number of subjects with at least one TEAE | 76 ( 4.2) | 91 | 70 ( 3.8) | 98 | 146 ( 4.0) | 189 |
| Alanine aminotransferase increased | 7 ( 0.4) | 8 | 9 ( 0.5) | 9 | 16 ( 0.4) | 17 |
| Ascites | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Aspartate aminotransferase increased | 5 ( 0.3) | 5 | 8 ( 0.4) | 9 | 13 ( 0.4) | 14 |
| Blood alkaline phosphatase increased | 0 ( 0.0) | 0 | 6 ( 0.3) | 6 | 6 ( 0.2) | 6 |
| Blood bilirubin increased | 4 ( 0.2) | 4 | 6 ( 0.3) | 6 | 10 ( 0.3) | 10 |
| Cholestasis | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Gamma-glutamyltransferase abnormal | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Gamma-glutamyltransferase increased | 18 ( 1.0) | 19 | 17 ( 0.9) | 17 | 35 ( 1.0) | 36 |
| Hepatic cancer | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Hepatic cirrhosis | 1 ( 0.1) | 1 | 3 ( 0.2) | 3 | 4 ( 0.1) | 4 |
| Hepatic cyst | 3 ( 0.2) | 3 | 2 ( 0.1) | 2 | 5 ( 0.1) | 5 |
| Hepatic encephalopathy | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Hepatic enzyme increased | 6 ( 0.3) | 8 | 8 ( 0.4) | 9 | 14 ( 0.4) | 17 |
| Hepatic fibrosis | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 | 2 ( 0.1) | 2 |
| Hepatic lesion | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Hepatic pain | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Hepatic steatosis | 14 ( 0.8) | 14 | 14 ( 0.8) | 14 | 28 ( 0.8) | 28 |
| Hepatomegaly | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Hyperbilirubinaemia | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 | 3 ( 0.1) | 3 |
| International normalised ratio increased | 7 ( 0.4) | 8 | 4 ( 0.2) | 4 | 11 ( 0.3) | 12 |
| Liver function test abnormal | 2 ( 0.1) | 2 | 2 ( 0.1) | 2 | 4 ( 0.1) | 4 |
| Liver function test increased | 4 ( 0.2) | 4 | 3 ( 0.2) | 3 | 7 ( 0.2) | 7 |
| Prothrombin time prolonged | 2 ( 0.1) | 2 | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 |
| Transaminases increased | 3 ( 0.2) | 3 | 0 ( 0.0) | 0 | 3 ( 0.1) | 3 |
| Haemangioma of liver | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Hepatitis | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Hepatocellular carcinoma | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Hypoalbuminaemia | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Oesophageal varices haemorrhage | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Portal hypertension | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Transaminases abnormal | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |

Source: ISS Table 14.3.2.1
Note: See Appendix 5 of the ISAP for details on the search terms used. Preferred terms are sorted by the total count first, then inclisiran, then placebo.
Abbreviations: E=Event Count; ISAP=Integrated Statistical Analysis Plan; TEAE=treatment-emergent adverse event

No additional safety concern was identified in the phase I and II studies.

*Diabetes and glycaemic control*

Overall, AEs associated with the development or worsening of diabetes mellitus were balanced between inclisiran and placebo. Slightly more AEs of HbA1c increased (placebo 0.2%, inclisiran 0.5%) and hyperglycaemia (0.8%, 1.4%) occurred in the inclisiran compared to the placebo group, but type 2 diabetes mellitus occurred more frequently on placebo (1.2%) than inclisiran (0.8%).

Results for subjects with diabetes mellitus at baseline were comparable between the inclisiran and the placebo group, while in subjects without diabetes mellitus at baseline numerically slightly more in the placebo (4.7%) than in the inclisiran group (4.4%) had a TEAE related to development of diabetes mellitus.

There were no clear clinically meaningful differences between placebo and inclisiran-treated subjects in shift from baseline in glucose control based on fasting glucose, HbA1c, and glucose control category using last on treatment values, but slightly more subjects in the inclisiran compared to the placebo group showed shifts towards a poorer outcome (overall: placebo worsened 21.7%, inclisiran 25.2%; placebo improved 2.3%, inclisiran 2.1%; placebo no change 74.9%, inclisiran 71.6%).

In subjects with no diabetes at baseline, new-onset of diabetes mellitus occurred in 4.7% on placebo and 4.3% on inclisiran. In subjects with impaired glucose tolerance at baseline, new-onset diabetes mellitus occurred in 13.8% on placebo and 14.6% on inclisiran. Time to new-onset diabetes was comparable between the placebo and the inclisiran groups.

*Cardiac Safety*

Based on assessments of AEs and vital signs, no significant difference in the cardiac safety profile was observed between the placebo and the inclisiran group.

**Table 3.3.8.6: Treatment-Emergent Cardiac Adverse Event in the Safety Pool**

| | Placebo (N=1822) | | Inclisiran (N=1833) | | Total (N=3655) | |
|---|---|---|---|---|---|---|
| Category | n (%) | E | n (%) | E | n (%) | E |
| MACE* | 172 ( 9.4) | 201 | 131 ( 7.1) | 141 | 303 ( 8.3) | 342 |
| CV Death | 14 ( 0.8) | 16 | 17 ( 0.9) | 18 | 31 ( 0.8) | 34 |
| Resuscitated Cardiac Arrest | 1 ( 0.1) | 1 | 4 ( 0.2) | 4 | 5 ( 0.1) | 5 |
| Non-Fatal MI | 142 ( 7.8) | 164 | 96 ( 5.2) | 102 | 238 ( 6.5) | 266 |
| Stroke (Ischemic or Hemorrhagic) | 18 ( 1.0) | 20 | 16 ( 0.9) | 17 | 34 ( 0.9) | 37 |

Source: ISS Table 14.3.1.17
* MACE (major cardiovascular event) is defined as the composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic or haemorrhagic).
Note: See Appendix 5 of the ISAP for details on the search terms used.
Abbreviation: CV=cardiovascular; E=Event Count; ISAP= Integrated Statistical Analysis Plan; MI=myocardial infarction

## *Serious adverse event/deaths/other significant events*

*Deaths*

The number and percentage of deaths occurring in the phase III trials was comparable between the placebo and the inclisiran group; no clear pattern or differences between these groups were observed in the phase III studies. However, death due to cardiac disorders occurred in 0.7% on inclisiran and 0.5% on placebo. The numbers are too small for any clear conclusion; a final conclusion will depend on the results of the CV outcome-study which will only be available post-licensing.

**Table 3.3.8.9: Summary of Deaths in the Safety Pool**

| Preferred Term | Placebo (N=1822) n (%) | E | Inclisiran (N=1833) n (%) | E | Total (N=3655) n (%) | E |
|---|---|---|---|---|---|---|
| Number of TEAEs with a Fatal Outcome | 27 ( 1.5) | 36 | 27 ( 1.5) | 29 | 54 ( 1.5) | 65 |
| Cardiac disorders | 9 ( 0.5) | 11 | 13 ( 0.7) | 14 | 22 ( 0.6) | 25 |
| Acute myocardial infarction | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Cardiac arrest | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Cardiac failure | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Cardiac failure congestive | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 | 2 ( 0.1) | 2 |
| Cardiomyopathy | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Coronary artery disease | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Coronary artery insufficiency | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Hypertensive heart disease | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Left ventricular failure | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 | 2 ( 0.1) | 2 |
| Myocardial infarction | 4 ( 0.2) | 4 | 4 ( 0.2) | 4 | 8 ( 0.2) | 8 |
| Myocardial ischaemia | 2 ( 0.1) | 2 | 1 ( 0.1) | 1 | 3 ( 0.1) | 3 |
| Ventricular fibrillation | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Ventricular tachyarrhythmia | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Gastrointestinal disorders | 2 ( 0.1) | 2 | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 |
| Ascites | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Intestinal ischaemia | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| General disorders and administration site conditions | 6 ( 0.3) | 6 | 4 ( 0.2) | 4 | 10 ( 0.3) | 10 |
| Cardiac death | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Death | 3 ( 0.2) | 3 | 3 ( 0.2) | 3 | 6 ( 0.2) | 6 |
| Multiple organ dysfunction syndrome | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Sudden cardiac death | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Infections and infestations | 4 ( 0.2) | 6 | 1 ( 0.1) | 1 | 5 ( 0.1) | 7 |
| Encephalitis | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Lower respiratory tract infection | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Pneumonia | 2 ( 0.1) | 2 | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 |
| Sepsis | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Septic shock | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Injury, poisoning and procedural complications | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Road traffic accident | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 6 ( 0.3) | 7 | 4 ( 0.2) | 5 | 10 ( 0.3) | 12 |
| Adenocarcinoma | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Bladder cancer | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Gastrointestinal lymphoma | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Gastrooesophageal cancer | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Hepatocellular carcinoma | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Lung adenocarcinoma | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Lung neoplasm malignant | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 | 2 ( 0.1) | 2 |
| Metastases to liver | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Metastatic carcinoma of the bladder | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Oesophageal carcinoma | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Nervous system disorders | 1 ( 0.1) | 1 | 1 ( 0.1) | 1 | 2 ( 0.1) | 2 |
| Cerebral haemorrhage | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Ischaemic stroke | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Respiratory, thoracic and mediastinal disorders | 2 ( 0.1) | 2 | 4 ( 0.2) | 4 | 6 ( 0.2) | 6 |
| Acute respiratory failure | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Chronic obstructive pulmonary disease | 0 ( 0.0) | 0 | 2 ( 0.1) | 2 | 2 ( 0.1) | 2 |
| Pneumonia aspiration | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |
| Pulmonary embolism | 0 ( 0.0) | 0 | 1 ( 0.1) | 1 | 1 ( 0.0) | 1 |
| Respiratory, thoracic and mediastinal disorders (Continued) | 2 ( 0.1) | 2 | 4 ( 0.2) | 4 | 6 ( 0.2) | 6 |
| Pulmonary oedema | 1 ( 0.1) | 1 | 0 ( 0.0) | 0 | 1 ( 0.0) | 1 |

Source: ISS Table 14.3.1.16
Abbreviations: E=Event Count; TEAE=treatment-emergent adverse event

In the phase II study ORION-1, 2 subjects died, 1 in the 500 mg inclisiran single-dose group due to MI and 1 in the 200 mg inclisiran double-dose group due to device-related infection. In study ORION-3, 1 subject in group 1 (inclisiran only arm) died. No deaths were reported for subjects treated with inclisiran in group 2 (switching arm).
No deaths were reported in study ORION-2 and the phase I studies.

*Other Serious Adverse Events*

Overall, serious AEs occurred more often in the placebo than the inclisiran group of the phase III trials; the incidence of treatment-emergent serious adverse events (TESAEs) was 23.0% (419/1822) in the placebo and 20.4% (374/1833) in the inclisiran group. There was no difference in the frequency or nature of TESAEs between groups. TESAEs were predominantly CV events and approximately half of these were considered severe. There were no imbalances of TESAE for neoplasms between groups [placebo 2.7% (49/1822); inclisiran 2.4% (44/1833)]. Details are given in the table below.

**Table 3.3.8.10: Common (≥0.5% Within Either Treatment Group) TESAEs Safety Pool**

| | Placebo (N=1822) | | Inclisiran (N=1833) | | Total (N=3655) | |
|---|---|---|---|---|---|---|
| **Preferred Term** | **n (%)** | **E** | **n (%)** | **E** | **n (%)** | **E** |
| Subject with at least one TESAE | 419 ( 23.0) | 763 | 374 ( 20.4) | 645 | 793 ( 21.7) | 1408 |
| Coronary artery disease | 33 ( 1.8) | 40 | 24 ( 1.3) | 24 | 57 ( 1.6) | 64 |
| Acute myocardial infarction | 31 ( 1.7) | 35 | 21 ( 1.1) | 22 | 52 ( 1.4) | 57 |
| Angina pectoris | 20 ( 1.1) | 21 | 21 ( 1.1) | 21 | 41 ( 1.1) | 42 |
| Angina unstable | 25 ( 1.4) | 27 | 16 ( 0.9) | 18 | 41 ( 1.1) | 45 |
| Pneumonia | 17 ( 0.9) | 17 | 21 ( 1.1) | 23 | 38 ( 1.0) | 40 |
| Atrial fibrillation | 15 ( 0.8) | 17 | 20 ( 1.1) | 22 | 35 ( 1.0) | 39 |
| Cardiac failure congestive | 22 ( 1.2) | 32 | 12 ( 0.7) | 12 | 34 ( 0.9) | 44 |
| Non-cardiac chest pain | 18 ( 1.0) | 18 | 14 ( 0.8) | 14 | 32 ( 0.9) | 32 |
| Chronic obstructive pulmonary disease | 12 ( 0.7) | 15 | 11 ( 0.6) | 13 | 23 ( 0.6) | 28 |
| Myocardial infarction | 10 ( 0.5) | 10 | 12 ( 0.7) | 12 | 22 ( 0.6) | 22 |
| Peripheral arterial occlusive disease | 10 ( 0.5) | 11 | 9 ( 0.5) | 9 | 19 ( 0.5) | 20 |
| Acute kidney injury | 9 ( 0.5) | 9 | 8 ( 0.4) | 9 | 817 ( 0.5) | 17 |

Source: ISS Table 14.3.1.5.1
Note: Includes AEs with onset after study treatment began.
Abbreviations: E=Event Count; TEAE=treatment-emergent adverse event

No additional serious AEs were identified in the phase I and II studies

## *Laboratory findings*

*Biochemical Markers of Hepatic Function*

Overall, no clinically meaningful changes in alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), or total bilirubin were reported in either the placebo or the inclisiran group over the course of the studies. There were no cases meeting the definition of Hy's Law in either group.

The percentages of subjects with ALT, ALP, and AST >3x ULN and total bilirubin >2x ULN were comparable between groups. Overall, 1.8% in each group (n=32 and 33, respectively) had at least 1 clinically significant chemistry laboratory value and 5 subjects on inclisiran and 3 on placebo had

increases >3x ULN in both ALT and AST. In both groups, the majority of elevated laboratory levels returned to their baseline levels with continued inclisiran or placebo treatment.

**Table 3.3.8.11: Incidence of Clinically Significant ALT, AST, Total Bilirubin, and Alkaline Phosphatase in the Safety Pool**

| Category | Placebo (N=1822) n (%) | Inclisiran (N=1833) n (%) | Total (N=3655) n (%) |
|---|---|---|---|
| Subjects with at least one Chemistry CS Lab value | 32 ( 1.8) | 33 ( 1.8) | 65 ( 1.8) |
| Alanine Aminotransferase(U/L) | | | |
| >3 x ULN | 7 ( 0.4) | 9 ( 0.5) | 16 ( 0.4) |
| >3 and <=5 x ULN | 6 ( 0.3) | 5 ( 0.3) | 11 ( 0.3) |
| >5 and <=10 x ULN | 1 ( 0.1) | 4 ( 0.2) | 5 ( 0.1) |
| >10 and <=20 x ULN | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| >20 x ULN | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Alkaline Phosphatase(U/L) | | | |
| >2 x ULN | 5 ( 0.3) | 8 ( 0.4) | 13 ( 0.4) |
| Aspartate Aminotransferase(U/L) | | | |
| >3 x ULN | 10 ( 0.5) | 8 ( 0.4) | 18 ( 0.5) |
| >3 and <=5 x ULN | 8 ( 0.4) | 5 ( 0.3) | 13 ( 0.4) |
| >5 and <=10 x ULN | 1 ( 0.1) | 3 ( 0.2) | 4 ( 0.1) |
| >10 and <=20 x ULN | 1 ( 0.1) | 0 ( 0.0) | 1 ( 0.0) |
| >20 x ULN | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| Bilirubin(mg/dL) | | | |
| >2 x ULN | 14 ( 0.8) | 14 ( 0.8) | 28 ( 0.8) |

Source: ISS Table 14.3.3.1.2.2
Note: Clinically significant criteria are met when both of the following occur:
- Post-baseline values meet the thresholds, and
- Baseline values or any prior post-baseline values do not meet the thresholds.
The worst post-baseline value was utilised in the analyses.
Abbreviations: CS=clinically significant; ULN=upper limit of normal

However, the percentages of subjects with potentially clinically significant (PCS; >1x to 3x ULN) elevations of ALT, as well as AST were higher in the inclisiran, than the placebo group [19.7% (361/1833) versus 13.6% (248/1822) and 17.2% (316/1833) versus 11.1% (202/1822), respectively].

According to the applicant, subjects with elevated biochemical markers of hepatic function will be followed in the long-term extension study ORION-8. These data will need to be analysed for a final conclusion on the influence of inclisiran on hepatic function.

*Biochemical Markers of Renal Function*

No clinically meaningful changes in serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) were observed in the placebo and inclisiran group over the course of the studies.

**Table 3.3.8.12: Incidence of Clinically Significant Serum Creatinine in the Safety Pool**

| Category* | Placebo (N=1822) n (%) | Inclisiran (N=1833) n (%) | Total (N=3655) n (%) |
|---|---|---|---|
| Subjects with at least one Chemistry CS Lab value | 93 ( 5.1) | 88 ( 4.8) | 181 (5.0) |
| Creatinine(mg/dL) | | | |
| >=50% increase from baseline (not >2m g/dL) | 54 ( 3.0) | 52 ( 2.8) | 106 (2.9) |
| >2 mg/dL | 39 ( 2.1) | 36 ( 2.0) | 75 (2.1) |
| >=50% increase from baseline or >2 mg/dL | 93 ( 5.1) | 88 ( 4.8) | 181 (5.0) |

Source: ISS Table 14.3.3.1.2.2
* Clinically significant criteria are met when both of the following occur:
- Post-baseline values meet the thresholds, and
- Baseline values or any prior post-baseline values do not meet the thresholds.
The worst post-baseline value will was utilised in the analyses.
Abbreviation: CS=clinically significant

*Biochemical Markers of Myopathy*

No clinically meaningful changes in creatinine kinase in either the placebo or the inclisiran group, nor significant imbalances in the percentages of subjects with clinically significant changes in creatinine kinase between the placebo and the inclisiran group were observed

Slightly more subjects in the inclisiran, than the placebo group had creatinine kinase >5x ULN, >5x and ≤10x ULN, and >10 and ≤20x ULN but numbers were small and no subject in the inclisiran group had elevations >20x ULN versus 4 in the placebo group. Furthermore, 1 subject in the placebo group had an associated TEAE (myalgia) compared to none in the inclisiran group. The majority subjects with normal baseline values remained within normal range (65.6% inclisiran, 64% placebo).

**Table 3.3.8.13: Incidence of Clinically Significant Creatinine Kinase in the Safety Pool**

| Category* | Placebo (N=1822) n (%) | Inclisiran (N=1833) n (%) | Total (N=3655) n (%) |
|---|---|---|---|
| Subjects with at least one Chemistry CS Lab value | 22 ( 1.2) | 24 ( 1.3) | 46 ( 1.3) |
| Creatine Kinase(U/L) | | | |
| >5 x ULN | 22 ( 1.2) | 24 ( 1.3) | 46 ( 1.3) |
| >5 and <=10 x ULN | 16 ( 0.9) | 20 ( 1.1) | 36 ( 1.0) |
| >10 and <=20 x ULN | 2 ( 0.1) | 4 ( 0.2) | 6 ( 0.2) |
| >20 x ULN | 4 ( 0.2) | 0 ( 0.0) | 4 ( 0.1) |

Source: ISS Table 14.3.3.1.2.2
* Clinically significant criteria are met when both of the following occur:
- Post-baseline values meet the thresholds, and
- Baseline values or any prior post-baseline values do not meet the thresholds.
The worst post-baseline value was utilised in the analyses.
Abbreviations: CS=clinically significant; ULN=upper limit of normal

*Inflammatory Markers (hsCRP)*

No clinically meaningful changes in hsCRP or shifts in mean and median hsCRP values were observed in either group.

*Haematology and Coagulation*

No clinically meaningful changes in haematology or coagulation parameters were reported for either group.

## *Safety in special populations*

*Age*

There were no significant differences in the TEAE and serious TEAE profiles of subjects in the inclisiran and the placebo group across all age subgroups. Overall, the number of patients who experienced AEs was higher in the older age groups, regardless of treatment.

**Table 3.3.8.14: Summary of TEAEs in Inclisiran treatment group by age groups - Controlled Phase III Safety pool (Safety population)**

| | Any age | | Age <65 year | | Age >=65 years | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Age 65-74 years | | Age 75-84 years | | Age 85+ years | | Total >=65 years | |
| | Inclisiran N=1833 | Placebo N=1822 | Inclisiran N=852 | Placebo N=882 | Inclisiran N=742 | Placebo N=688 | Inclisiran N=231 | Placebo N=245 | Inclisiran N=8 | Placebo N=7 | Inclisran (N=981) | Placebo (N=940) |
| **MedDRA terms** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** |
| **Total TEAEs** | 1430 (78.0) | 1409 (77.3) | 651 (76.4) | 656 (74.4) | 584 (78.7) | 537 (78.1) | 188 (81.4) | 210 (85.7) | 7 (87.5) | 6 (85.7) | 779 (79.4) | 753 (80.1) |
| **Serious TEAEs – Total** | 374 (20.4) | 419 (23.0) | 142 (16.7) | 179 (20.3) | 163 (22.0) | 154 (22.4) | 67 (29.0) | 83 (33.9) | 2 (25.0) | 3 (42.9) | 232 (23.6) | 240 (25.5) |
| **Death** | 27 (1.5) | 27 (1.5) | 11 (1.3) | 9 (1.0) | 12 (1.6) | 8 (1.2) | 4 ( 1.7) | 10 ( 4.1) | 0 ( 0.0) | 0 ( 0.0) | 16 (1.6) | 18 (1.9) |
| **TEAE leading to study treatment discontinuation** | 45 (2.5) | 35 (1.9) | 13 (1.5) | 16 (1.8) | 22 (3.0) | 12 (1.7) | 10 (4.3) | 7 (2.9) | 0 (0.0) | 0 (0.0) | 32 (3.3) | 19 (2.0) |
| **Psychiatric disorders - SOC** | 83 (4.5) | 86 (4.7) | 43 (5.0) | 43 (4.9) | 30 (4.0) | 32 (4.7) | 10 (4.3) | 11 (4.5) | 0 (0.0) | 0 (0.0) | 40 (4.1) | 43 (4.6) |
| **Nervous system disorders- SOC** | 275 (15.0) | 265 (14.5) | 107 (12.6) | 107 (12.1) | 118 (15.9) | 112 (16.3) | 49 (21.2) | 44 (18.0) | 1 (12.5) | 2 (28.6) | 168 (17.1) | 158 (16.8) |
| **Accidents and injuries - SMQ** | 194 (10.6) | 196 (10.8) | 72 (8.5) | 84 (9.5) | 78 (10.5) | 74 (10.8) | 44 (19.0) | 37 (15.1) | 0 (0.0) | 1 (14.3) | 122 (12.4) | 112 (11.9) |
| **Cardiac disorders - SOC** | 261 (14.2) | 300 (16.5) | 103 (12.1) | 130 (14.7) | 114 (15.4) | 113 (16.4) | 41 (17.7) | 55 (22.4) | 3 (37.5) | 2 (28.6) | 158 (16.1) | 170 (18.0) |
| **Vascular disorders - SOC** | 187 (10.2) | 209 (11.5) | 69 (8.1) | 78 (8.8) | 79 (10.6) | 93 (13.5) | 38 (16.5) | 38 (15.5) | 1 (12.5) | 0 (0.0) | 118 (12.0) | 131 (13.9) |
| **Cerebrovascular disorders - SMQ** | 45 (2.5) | 47 (2.6) | 9 (1.1) | 21 (2.4) | 26 (3.5) | 15 (2.2) | 9 (3.9) | 11 (4.5) | 1 (12.5) | 0 (0.0) | 36 (3.7) | 26 (2.8) |
| **Infections and infestations - SOC** | 651 (35.5) | 612 (33.6) | 301 (35.3) | 290 (32.9) | 258 (34.8) | 231 (33.6) | 87 (37.7) | 89 (36.3) | 5 (62.5) | 2 (28.6) | 350 (35.7) | 322 (34.3) |
| **Anticholinergic syndrome- SMQ** | 110 (6.0) | 113 (6.2) | 39 (4.6) | 43 (4.9) | 49 (6.6) | 48 (7.0) | 21 (9.1) | 19 (7.8) | 1 (12.5) | 3 (42.9) | 71 (7.2) | 70 (7.4) |
| **Quality of life decreased*** | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0(0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

| | Any age | | Age <65 year | | Age >=65 years | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Age 65-74 years | | Age 75-84 years | | Age 85+ years | | Total >=65 years | |
| | Inclisiran N=1833 | Placebo N=1822 | Inclisiran N=852 | Placebo N=882 | Inclisiran N=742 | Placebo N=688 | Inclisiran N=231 | Placebo N=245 | Inclisiran N=8 | Placebo N=7 | Inclisran (N=981) | Placebo (N=940) |
| **MedDRA terms** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** |
| **Sum of postural, falls, black outs, syncope,dizziness, ataxia, fractures**** | 162 (8.8) | 151 (8.3) | 51 (6.0) | 55 (6.2) | 68 (9.2) | 70 (10.2) | 43 (18.6) | 25 (10.2) | 0(0.0) | 1 (14.3) | 111 (11.3) | 96 (10.2) |

*PTs: Quality of life decreased, impaired quality of life
**PTs: orthostatic hypotension, fall, loss of consciousness, syncope, dizziness, ataxia, and all PTs containing 'fracture'
Source: [Table 3-1.2.1p1] and [Table 3-1.2.2.p1]

Table **3.3.8.15:** Summary of SAEs in Inclisiran treatment group by age groups - Controlled Phase III Safety pool (Safety population)

| | Age <65 year | | Age 65-74 years | | Age 75-84 years | | Age 85+ years | | Unknown | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Inclisiran | Placebo | Inclisiran | Placebo | Inclisiran | Placebo | Inclisiran | Placebo | Inclisiran | Placebo | Inclisran | Placebo |
| | n* (%) | n* (%) | n* (%) | n* (%) | n* (%) | n* (%) | n* (%) | n* (%) | n* (%) | n* (%) | n* (%) | n* (%) |
| **Disability or permanent damage** | 1 (0.12) | 3 (0.34) | 7 (0.94) | 4 (0.58) | 3 (1.30) | 1 (0.41) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 11 (0.60) | 8 (0.44) |
| **Hospitalization New/Hospitalisation Prolonged** | 123 (14.4) | 151 (17.12) | 145 (19.54) | 151 (21.95) | 60 (25.97) | 71 (28.98) | 6 (75.0) | 5 (71.42) | 2 (100.0) | 2 (100.0) | 336 (18.31) | 380 (20.83) |
| **Life threatening** | 6 (0.7) | 11 (1.25) | 8 (1.08) | 11 (1.60) | 4 (1.73) | 7 (2.86) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 18 (0.98) | 29 (1.59) |
| **Other Serious (Important Medical Events)** | 15 (1.76) | 19 (2.15) | 33 (4.45) | 32 (4.65) | 16 (6.93) | 22 (8.98) | 2 (25.0) | 1 (14.29) | 0 (0.0) | 0 (0.0) | 66 (3.60) | 74 (4.12) |

*Distinct Count of Subject No
Source: Data generated from the SAEs captured in the safety database – [Annex 1-Safety database]

*Gender*

No significant differences between female and male subjects were identified in the analyses of TEAE and serious TEAE in the inclisiran and the placebo group.

*Race / Ethnicity*

Subgroup analyses by race / ethnicity did not reveal significant differences for the predefined groups, but the number of subjects in subgroups other than 'White' or 'Not Hispanic or Latino' are limited [Race (n placebo, inclisiran): White 1704, 1669; Black 101, 131; Other 17, 33; Ethnicity: Hispanic or Latino 116, 120; Not Hispanic or Latino 1706, 1713] and no definite conclusions on AEs by race / ethnicity are possible. So far there is no clinical evidence indicating differences in the efficacy or safety of inclisiran based on ethnicity and available clinical data of other PCSK9 inhibitors (antibodies) support the assumption that efficacy and safety of these medicinal products do not differ by race / ethnicity.

*Renal Function*

Subgroup analyses by normal, mild, and moderate renal impairment did not reveal significant differences between placebo and inclisiran; for the subgroup of severe renal impairment, the number of subjects is too small for a definite conclusion.

*Hepatic Function*

Analyses of AEs by hepatic impairment is primarily based on safety results from the single-dose, open-label, hepatic impairment study ORION-6. This study enrolled 28 subjects, 10 with mild hepatic impairment, 6 with moderate hepatic impairment, and 12 healthy subjects with normal hepatic

function matched to the subjects with hepatic impairment; 1 subject was withdrawn by the sponsor due to entry into a mandatory in house treatment program and was therefore unavailable following the day 120 visit.

According to the applicant hepatic function status was not assessed as part of the study protocol for the pivotal phase III trials, but the applicant has provided a post-hoc classification of the hepatic function of subjects in the phase III safety pool based on the Child-Pugh hepatic function scoring system. According to this post-hoc assignment, the majority of subjects were ascribed a Child-Pugh score of 5 (n=3595) or of 6 (n=52), only a few subjects (n=4) of 7, and no subject of > 7. The analyses of AEs by hepatic function according to this post-hoc classification has not revealed relevant differences between inclisiran and placebo treated subjects although the interpretation is limited by the post-hoc assignment of the score as well as the low number of subjects with a Child-Pugh score > 5; subjects with severe hepatic impairment have not been studied which is reflected in the PI.

## *Immunological events*

*Anti-drug Antibodies*

Samples tested positive for anti-drug antibodies (ADA) occurred at low frequency and were comparable at pre- and post-dose timepoints; overall, titres were low. No associations between the presence of ADA and AEs or changes in LDL-C and PSCK9 levels were identified.

According to the applicant, the development of ADA will continue to be evaluated in the ongoing long-term extension studies ORION-3 and ORION-8 and the CV outcomes trial ORION-4.

*Hypersensitivity*

No systemic allergic reactions or signs or symptoms suggestive of systemic allergic reactions were observed with the administration of inclisiran. TEAEs related to hypersensitivity did not indicate differences between groups except for events at the injection site.

## *Safety related to drug-drug interactions and other interactions*

Inclisiran is not a substrate, inhibitor, or inducer of cytochrome P450 enzymes or common drug transporters and therefore not expected to have clinically significant interactions with other medicinal products. Statin drug-drug interaction assessments demonstrated a lack of clinically meaningful interactions with either atorvastatin or rosuvastatin.

## *Discontinuation due to adverse events*

No difference in the frequency or nature of TEAEs leading to discontinuation of study drug was identified between the inclisiran and the placebo group, except for subjects withdrawn from study drug due to TEAEs at the injection site [placebo 0% (0/1822); inclisiran 0.2% (4/1833)].

## *Post marketing experience*

N/A

## 2.6.1. Discussion on clinical safety

The safety data set for the current application is primarily based on pooled safety results from the 3 confirmatory, randomised, double-blind, 18-month, placebo-controlled phase III studies ORION-9 [Heterozygous familial hypercholesterolemia (HeFH)], ORION-10 [Atherosclerotic cardiovascular disease (ASCVD)], and ORION-11 (ASCVD and ASCVD risk equivalents), comprising about 3600 subjects treated for more than a year. Thus, patient exposure in the pivotal trials is considered extensive comprising about 1700 subjects in each the inclisiran and the placebo group treated for 18 months. Safety of inclisiran given for more than 18 months of treatment is currently under evaluation including a CV outcomes trial.

Dropouts were low in the inclisiran, as well as the placebo group with 94.4% and 92.8%, respectively, completing the phase III studies, and 90.9% and 90.6%, respectively, receiving all 4 doses of study drug. Demographic characteristics, relevant CV risk factors and other comorbidities, lipid-modifying therapy usage, and recorded previous and concomitant medications taken at randomisation were sufficiently balanced between treatment groups. About one third of the subjects included in the Safety Pool were female.

Overall, in the phase III trials the incidence and type of common AEs was comparable between the placebo and the inclisiran group.

The number and percentage of deaths was comparable between the placebo and the inclisiran group, but numbers are too small for clear conclusions; a final conclusion will depend on the results of the CV outcome-study which will become available post-licensing.

The incidence of severe AEs was higher on placebo than inclisiran (15.3% versus 13.0%); the most common severe AEs were acute MI (1.5%, 0.8%), coronary artery disease (0.9%, 1.0%), and cardiac failure congestive (0.6%, 0.4%). Likewise, overall serious AEs occurred more often in the placebo than the inclisiran group, but there were no clear differences in the frequency or nature of AEs between groups. Serious AEs were predominantly CV events and approximately half of these were considered severe.

The most common AEs occurring more frequently on inclisiran than placebo were diabetes mellitus, nasopharyngitis, arthralgia, back pain, urinary tract infection, diarrhoea, bronchitis, cough, headache, angina pectoris, dizziness, pain in extremity, dyspnoea, and injection site reaction, while osteoarthritis, blood CPK increase, non-cardiac chest pain, and influenza occurred more frequently on placebo than inclisiran. However, except for injection site AEs (placebo 1.8%; inclisiran 8.2%) these differences between groups were small.

Injection site AEs were localised, predominantly mild or occasionally moderate, transient, and resolved without sequelae; no subject on inclisiran had a severe or serious injection site AE.

Overall, AEs associated with the development or worsening of diabetes mellitus were balanced between inclisiran and placebo. Slightly more AEs of HbA1c increased (placebo 0.2%, inclisiran 0.5%) and hyperglycaemia (0.8%, 1.4%) occurred in the inclisiran compared to the placebo group, but type 2 diabetes mellitus occurred more frequently on placebo (1.2%) than inclisiran (0.8%). Results for subjects with diabetes mellitus at baseline were comparable between the inclisiran and the placebo group, while in subjects without diabetes mellitus at baseline numerically slightly more in the placebo (4.7%) than in the inclisiran group (4.4%) had a TEAE related to development of diabetes mellitus. There were no clear clinically meaningful differences between placebo and inclisiran-treated subjects in shift from baseline in glucose control based on fasting glucose, HbA1c, and glucose control category using last on treatment values, but slightly more subjects in the inclisiran compared to the placebo group showed shifts towards a poorer outcome. In subjects with no diabetes at baseline, new-onset of

diabetes mellitus occurred in 4.7% on placebo and 4.3% on inclisiran. In subjects with impaired glucose tolerance at baseline, new-onset diabetes mellitus occurred in 13.8% on placebo and 14.6% on inclisiran. Time to new-onset diabetes was comparable between the placebo and the inclisiran groups.

Overall, no clinically meaningful changes in biochemical markers of hepatic function were identified in either group; the percentages of subjects with clinically relevant elevations of these markers were comparable between groups and in both groups, the majority of elevated laboratory levels returned to their baseline levels with continued inclisiran or placebo treatment. However, the percentages of subjects with potentially clinically significant elevations of ALT, as well as AST were higher in the inclisiran, than the placebo group (19.7% versus 13.6% and 17.2% versus 11.1%, respectively). There were no cases meeting the definition of Hy's Law. According to the applicant, subjects with elevated biochemical markers of hepatic function will be followed in the long-term extension study ORION-8.

AEs associated with hepatic safety appear to be balanced between the placebo and the inclisiran group.

As regards biochemical markers of myopathy, no clinically meaningful changes or significant imbalances were observed. Slightly more subjects in the inclisiran, than the placebo group had creatinine kinase >5x ULN, >5x and ≤10x ULN, and >10 and ≤20x ULN but numbers were small and no subject in the inclisiran group had elevations >20x ULN versus 4 in the placebo group. Furthermore, 1 subject in the placebo group had an associated TEAE (myalgia) compared to none in the inclisiran group. The majority subjects with normal baseline values remained within normal range (65.6% inclisiran, 64% placebo).

No significant differences between the placebo and the inclisiran group were observed in the cardiac safety profile, for neurological events and neurocognitive disorders, ophthalmological AEs, AEs associated with renal safety, biochemical markers of renal function, changes in hsCRP or shifts in mean and median hsCRP values, changes in haematology or coagulation parameters, and between the commercial presentation prefilled syringe and the vial and syringe used in earlier clinical studies.

As regards safety in special populations, no significant differences in TEAE and serious TEAE related to age or gender were identified and subgroup analyses by race / ethnicity did not reveal significant differences for the predefined groups, but currently the number of subjects in subgroups other than 'White' are limited Subgroup analyses by normal, mild, and moderate renal impairment did not reveal significant differences between placebo and inclisiran; for the subgroup of severe renal impairment, the number of subjects is too small for a definite conclusion. Analyses of AEs by hepatic function for the Safety Pool are based on a post-hoc classification of the hepatic function of subjects in the phase III safety pool based on the Child-Pugh hepatic function scoring system, since hepatic function status was not assessed as part of the study protocol for the pivotal phase III trials. The analysis of AEs by hepatic function according to this post-hoc classification has not revealed relevant differences between inclisiran and placebo treated subjects although the interpretation is limited by the post-hoc assignment of the score as well as the low number of subjects with a Child-Pugh score >5; subjects with severe hepatic impairment have not been studied which is reflected in the agreed Product Information.

Anti-drug antibodies (ADA) occurred at low frequency and were comparable at pre- and post-dose timepoints. No associations between ADA and AEs, changes in LDL-C, or PSCK9 levels were identified. According to the applicant, the development of ADA will continue to be evaluated in the ongoing long-term extension studies and the CV outcomes trial. Also, no systemic allergic reactions or signs or symptoms suggestive of systemic allergic reactions were observed with the administration of inclisiran. TEAEs related to hypersensitivity did not indicate differences between groups except for events at the injection site.

As regards safety related to drug-drug interactions and other interactions, based on the available data, no clinically relevant interactions with other medications are expected.

No difference in the frequency or nature of TEAEs leading to discontinuation of study drug was identified between both groups, except for subjects withdrawn from study drug due to TEAEs at the injection site (placebo 0%, inclisiran 0.2%).

No additional safety concerns were identified in the phase I and II studies.

No post marketing data are currently available.

## 2.6.2. Conclusions on the clinical safety

The safety profile appears to be comparable between inclisiran and placebo when given in addition to maximal tolerated HMG-CoA reductase inhibitor (statin) therapy (including no statin in case of statin intolerance) and standard of care in the included patient populations (heterozygous familial hypercholesterolemia, atherosclerotic cardiovascular disease, atherosclerotic cardiovascular disease risk equivalents). The safety data set for the current application is extensive, comprising about 1700 subjects in each the inclisiran and the placebo group treated for 18 months; safety of inclisiran given for more than 18 months of treatment is currently under evaluation including a CV outcome trial. Treatment compliance in the 3 pivotal phase III trials was high and the number of drop outs low.

So far, no signs of adverse effects of inclisiran on cardiovascular morbidity or mortality have been identified. Numbers of AEs related to cardiovascular morbidity and mortality are low; relevant clinical trials are ongoing and results will be provided post-authorisation.

The number of deaths was low and comparable between both groups. Severe and serious adverse events occurred slightly more often in the placebo, than the inclisiran group, but there were no clear differences in the frequency or nature of AEs between groups.

Overall, in the phase III trials the incidence and type of common AEs was comparable between the placebo and the inclisiran group and differences between groups were small, except for injection site AEs (placebo 1.8%; inclisiran 8.2%). Injection site AEs were localised, predominantly mild or occasionally moderate, transient, and resolved without sequelae; no subject on inclisiran had a severe or serious injection site AE.

No significant effects of inclisiran on known safety issues identified with other lipid lowering therapies, such as liver disorders, renal disorders, diabetes, and musculoskeletal disorders, have been identified, but slightly more subjects in the inclisiran compared to the placebo group showed shifts towards a poorer outcome in AEs associated with the development or worsening of diabetes mellitus and potentially clinically significant elevations of ALT (19.7% vs. 13.6%) or AST (17.2% vs. 11.1%). According to the applicant, subjects with elevated biochemical markers of hepatic function will be followed in the long-term extension study ORION-8.

No significant differences in TEAE and serious TEAE related to age, gender, race / ethnicity, and hepatic or renal safety have been identified.

Anti-drug antibodies (ADA) occurred at low frequency and were comparable at pre- and post-dose timepoints. No associations between ADA and AEs, changes in LDL-C, or PSCK9 levels have been identified.

Overall, based on the data provided the safety profile of inclisiran is considered acceptable.

## 2.7. Risk Management Plan

### Safety concerns

Summary of the safety concerns

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | Long term safety<br>Use in pregnancy and breast-feeding<br>Use in patients with severe hepatic impairment |

### Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

| Study status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| None. | | | | |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| None. | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| **CKJX839A12201E1 (ORION-3)**: An open label, active comparator extension trial to assess the effect of long-term dosing of inclisiran and evolocumab given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C.<br>**Status**: Ongoing | To further characterize the long-term safety and tolerability of inclisiran (AEs, SAEs, Physical examination, CV events (including CV deaths) and laboratory evaluations. | Long -term safety | Final CSR: | 30 June 2022 |
| **CKJX839A12306B (ORION-8):** A long | To evaluate the safety and | Long-term safety | Final CSR: | 31 December 2023 |

| | | | | |
|---|---|---|---|---|
| term extension trial of the Phase III lipid-lowering trials to assess the effect of long-term dosing of inclisiran given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C.<br><br>**Status**: Ongoing | tolerability profile of long-term use of inclisiran. | | | |
| **Inclisiran Pregnancy outcomes Intensive Monitoring** (PRIM)<br><br>**Status**: Planned | The overall objective of the inclisiran PRIM program is to collect data on pregnancy outcomes in patients treated with inclisiran during pregnancy or prior to pregnancy<br><br>(including congenital malformations, spontaneous abortions, stillbirths and other adverse birth outcomes) as well as infant outcomes at 3 and 12 months postdelivery, including breast-feeding status and exposures, neonatal and infant deaths and developmental delays. The findings from this program will be used to evaluate the missing information 'Use | Use in pregnancy and breastfeeding. | Interim progress reports:<br><br>Final report Submission: | Annual interim progress reports will be provided with PSURs.<br><br>31 July 2031 The PRIM NIS will apply until a maximum of 10 years from the first launch or 500 prospectively reported live births with known status of malformations, whichever occurs first. |

| | | | | |
|---|---|---|---|---|
| | in pregnancy and breastfeeding', according to the RMP. | | | |

## *Risk minimisation measures*

Summary of risk minimisation measures and pharmacovigilance activities by safety concerns

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Long-term safety | **Routine risk minimization measures**: SmPC section: None; PL section: None<br><br>**Additional risk minimization measures**: None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None<br><br>**Additional pharmacovigilance activities**: Study CKJX839A12201E1 (ORION-3); (Date of final CSR (planned): 30-Jun-2022) |
| Use in pregnancy and breastfeeding | **Routine risk minimization measures:** SmPC section: 4.6; PL section: 2<br><br>**Additional risk minimization measures:** None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None<br><br>**Additional pharmacovigilance activities:** PRIM study (Date of final CSR (planned): 31-Jul-2031)<br><br>The PRIM NIS will apply until a maximum of 10 years from the first launch or 500 prospectively reported live births with known status of malformations, whichever occurs first. |
| **Use in patients with severe hepatic impairment** | **Routine risk minimization measures:** SmPC section: 4.2, 4.4, 5.2; PL section: 2<br><br>**Additional risk minimization measures:** None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None<br><br>**Additional pharmacovigilance activities:** None |

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

## *2.8. Pharmacovigilance*

### *Pharmacovigilance system*

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

## *2.9. New Active Substance*

The applicant compared the structure of inclisiran with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers inclisiran to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union

## *2.10. Product information*

### 2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Leqvio (inclisiran) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Primary hypercholesterolemia by definition is any hypercholesterolaemia, which is caused by a disturbance in the lipid metabolism (familial- or nonfamilial) and is not caused by another condition, such as hypothyroidism, or a drug effect. The heterozygous familial form of this condition (HeFH) is rare and is estimated to occur in 1:500 individuals globally. LDL-C levels in affected individuals are elevated and, in spite of aggressive statin use, there is still a 2-fold excess of CHD-related deaths relative to age-matched controls within this population[4].

Hypercholesterolaemia is characterised by an increased level of cholesterol in the blood. Primary hyperlipidaemia is usually due to genetic causes (monogenetic or polygenetic) and environmental factors, such as diet and lifestyle, and primary nonfamilial hyperlipidaemia is a kind of hyperlipidaemia that is not due to a specific genetic disorder, but due to polygenetic influences. Mixed dyslipidaemia is generally defined as elevated LDL-C and high triglycerides and/or low HDL-C.

A strong positive correlation and causal relationship between LDL-C level and risk of CHD has been derived from a large body of clinical and epidemiological data. There is also a strong relationship to other clinical manifestations in the body like cerebrovascular disease (i.e. ischaemic stroke) or peripheral vascular disease. Numerous clinical studies demonstrated that LDL-C lowering therapy especially with statins reduces the risk for CVD and epidemiologic data indicate a continuous increasing relative risk of CVD from very low to high levels of LDL-C, with a higher absolute risk in patients at the higher end of LDL-C levels.

Aim of any therapy in hypercholesterolaemia is to reduce LDL-C levels and to achieve LDL-C <70 mg/dL in patients with a history of multiple major ASCVD events or 1 major ASCVD event and other risks, and adding non-statins to achieve an LDL-C <100 mg/dL in severe primary hypercholesterolaemia (diagnostic LDL-C level ≥190 mg/dL), including familial hypercholesterolaemia (FH)[5, 6].

### 3.1.2. Available therapies and unmet medical need

Gold standard in the therapy for patients with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia to reduce LDL-C, as an adjunct to diet, are statins. Statins have robustly demonstrated CVD benefits in patients at increased CVD risk and clinical guidelines strongly recommend the use of statins in patients with elevated LDL-C levels. If baseline levels are between 1.8 mmol/L and 3.5 mmol/L (70 mg/dL and 135 mg/dL) treatment aims are to reduce LDL-C

[4] Akioyamen LE1, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, Tu JV. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open. 2017 Sep 1;7(9):e016461. doi: 10.1136/bmjopen-2017-016461.

[5] Grundy SM, Stone NJ, Bailey AL et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082e1143. DOI: 10.1161/CIR.0000000000000625

[6] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz455.

levels below 1.8 mmol/L (70 mg/dL) or at least to reduce LDL-C by 50%. There is a need for additional therapies for LDL C lowering and CVD prevention in patients at very high risk of CV events who are already receiving a maximum tolerated dose of a statin or have limitations in statin tolerability and do not reach LDL-C goals. There is no consensus definition for statin intolerance, but there should be documented evidence of intolerance due to emerging AEs to at least 2 different statins administered in doses required to achieve the target LDL-C level. Statin-associated adverse effects (e.g. muscular adverse effects) may occur that limit the ability to take a statin or a high enough dose of statin to reach the required LDL-C goal. These subjects are at a higher risk of not achieving their individual LDL-C target appropriate to their level of CV risk as other lipid-lowering therapies with non-statins, with the exception of PCSK9 inhibitors, only provide about 15-20% reduction in LDL-C levels.

Lipid-lowering therapy with ezetimibe and PCSK9 inhibitors achieve an additional LDL-C lowering. These drugs are indicated in subjects with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet to reduce LDL-C as an on-top therapy to statins when additional LDL-C lowering is needed as second line therapy (according to learned society guidelines).

Ezetimibe has demonstrated CVD benefit in the IMPROVE-IT trial[7], even if the absolute CV benefit from adding ezetimibe was limited in line with its modest effect on LDL-C. PCSK9 inhibitors lower LDL-C levels very effectively by over 50% and have also demonstrated CVD risk reduction in clinical trials in patients with established CVD[8, 9].

The CVD benefit of other lipid lowering therapies (i.e. fibrates) have not been demonstrated although even these medicinal products may provide a reduction of some lipid parameters including moderate reductions in LDL-C.

### 3.1.3. Main clinical studies

The phase III programme to investigate the effects of inclisiran in patients with HeFH and ASCVD or ASCVD-risk equivalents with elevated LDL-C levels despite maximally tolerated statin therapy include 3 randomised, double-blind, placebo-controlled, parallel-group studies:

- ORION-9 (n=482), a 540 Days randomised, double-blind, parallel group, multicentre study to evaluate the efficacy and safety of inclisiran 300 mg SC compared to placebo added to background LMT in patients with HeFH and elevated LDL-C.
- ORION-10 (n=1,571), a 540 Days randomised, double-blind, parallel group, multicentre study to evaluate the efficacy and safety of inclisiran 300 mg SC compared to placebo added to background LMT in patients with ASCVD and elevated LDL-C.
- ORION-11 (=1,617), a 540 Days randomised, double-blind, parallel group, multicentre study to evaluate the efficacy and safety of inclisiran 300 mg SC compared to placebo added to background LMT in patients with ASCVD or ASCVD- risk equivalents and elevated LDL-C.

[7] Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes.N Engl J Med. 2015; 372:2387–2397. doi: 10.1056/NEJMoa1410489.
[8] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-1722.
[9] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018 Nov 29;379(22):2097-2107.

## 3.2. Favourable effects

Inclisiran is a chemically modified double-stranded 21-23mer siRNA, conjugated on the sense strand with triantennary GalNAc to facilitate uptake by hepatocytes. In hepatocytes, the antisense strand is incorporated in the RISC and directs catalytic breakdown of mRNA for PCSK9. This inhibits the translation of PCSK9 protein, reduces the intrahepatic PCSK9, and increases LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation.

Inclisiran sodium at a dose of 300 mg (equivalent to 284 mg inclisiran) SC at Day 1, Day 90, and every 180 days thereafter lowers LDL-C by about 50% or more. This lipid-lowering is robust and statistically significant and is stable over the time with a slow returning of LDL-C to the baseline level after stopping the therapy by about 3% per month.

Data from the 3 confirmatory studies demonstrated that significantly more patients reached LDL-C targets of 2.5 mmol/L and 1.8 mmol/L and had ≥50% LDL-C lowering on inclisiran than on placebo [-49.52 (95% CI: -55.04, -43.99; p<0.0001) and -44.30 (95% CI: -48.48, -40.12; p<0.0001)] co-primary endpoints study ORION-9; -57.64 (95% CI: -60.86, -54.43; p<0.0001) and -53.78 (95% CI: -56.23, -51.33; p<0.0001) study ORION-10; -53.50 (95% CI: -56.66, -50.35; p<0.0001) and -49.92 (95% CI: -52.29, -47.55; p<0.0001) study ORION-11, respectively], signalling the clinical effectiveness of inclisiran therapy. Efficacy was supported by significant reductions in other relevant parameters of the cholesterol profile (i.e. PCSK9 (60% to 70%), TC (25% to 34%), Apo-B (33% to 43%), and non-HDL (35% to 43%).

The LDL-C effect of inclisiran was consistent across several subgroups, i.e. age, race, gender, ethnicity, region, metabolic disease, various genotyping, baseline BMI, baseline LDL-C, intensity of statin treatment, non-statin lipid-lowering therapy, and baseline GFR category. A sustained effect of LDL-C reduction has been demonstrated up to 540 days in the 3 placebo-controlled studies on top of statin therapy. Subgroup analyses demonstrated that the effect on LDL-C was independent of the intensity of the statin therapy.

Subgroup analyses have been presented across the age categories of <65 years - 74 years, 75 – 84 years, and ≥85 years, respectively, which was consistent with those seen in the overall population. Even that there was only a small number of elderly 85+ years, it could be demonstrated that inclisiran was just as effective as in the other groups observed in reducing the lipid parameters.

## 3.3. Uncertainties and limitations about favourable effects

Inclisiran has demonstrated its ability to reduce LDL-C in patients with elevated LDL-C levels, which is an approved surrogate marker for CVD risk. However, a favourable impact on CV outcomes has not yet been confirmed. Preliminary data from the 3 confirmatory studies on MACE (composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke [ischaemic or haemorrhagic]) show that it was equally distributed (ORION-9) or in favour of inclisiran (ORION-10, ORION-11). An analysis of these findings has currently not been provided. However, the overall number of events was low precluding firm conclusions.

The vast majority of participants in the 3 studies were White. Only a small group of Asians and Black people were included in the phase III studies. In regard of the Black population the efficacy data was consistent with the White population for the primary and key secondary endpoints. The same was evident for the small number of the Asian population included in the 3 pivotal studies.

Furthermore, the effect of inclisiran in LDL-C lowering has been demonstrated up to 18 month and not yet beyond.

## 3.4. Unfavourable effects

Overall, in the phase III trials the incidence and type of common AEs was comparable between the placebo and the inclisiran group.

Unfavourable effects associated with inclisiran in the placebo-controlled pivotal trials were adverse events reactions at the injection site (placebo 1.8%; inclisiran 8.2%); these adverse events were localised, predominantly mild or occasionally moderate, transient, and resolved without sequelae. No subject on inclisiran had a severe or serious injection site AE. The most frequently occurring adverse events at the injection site in patients treated with inclisiran were injection site reaction (3.1%), injection site pain (2.2%), injection site erythema (1.6%), and injection site rash (0.7%).

Furthermore, while no clinically meaningful changes (>3x ULN) in biochemical markers of hepatic function were identified in either group and the percentages of subjects with clinically relevant elevations of these markers were comparable between groups, the percentages of subjects with potentially clinically significant elevations (>1x to 3x ULN) of ALT, as well as AST were higher in the inclisiran, than the placebo group (19.7% versus 13.6% and 17.2% versus 11.1%, respectively). AEs associated with hepatic safety are balanced between the placebo and the inclisiran group.

## 3.5. Uncertainties and limitations about unfavourable effects

The number and percentage of deaths was comparable between the placebo and the inclisiran group, but numbers are too small for clear conclusions and the duration of treatment is limited to 18 months. In addition, no definite data on cardiovascular morbidity and mortality are currently available. Numbers of AEs related to cardiovascular morbidity and mortality are low and the available data do not indicate a detrimental effect of inclisiran on cardiovascular outcomes. A relevant CV outcome trial is ongoing and results will be provided post-authorisation.

No safety issues identified with other lipid lowering therapies, such as liver disorders, renal disorders, diabetes, and musculoskeletal disorders, have been identified with inclisiran, but slightly more subjects in the inclisiran compared to the placebo group showed shifts in AEs associated with the development or worsening of diabetes mellitus.

Besides injection site reactions, the most common AEs occurring more frequently on inclisiran than placebo were development or worsening of diabetes mellitus, nasopharyngitis, arthralgia, back pain, urinary tract infection, diarrhoea, bronchitis, cough, headache, angina pectoris, dizziness, pain in extremity, dyspnoea, while osteoarthritis, blood CPK increase, non-cardiac chest pain, and influenza occurred more frequently on placebo than inclisiran, but differences between groups for these unfavourable effects were small, not indicating clinically relevant differences and may well be due to random variation.

As regards safety in special populations, for subgroup analyses by race / ethnicity the number of subjects in subgroups other than 'White' are limited, but data so far do not indicate significant differences.

Analyses of AEs by hepatic function for the phase III studies Safety Pool are based on a post-hoc classification of the hepatic function. This analysis has not revealed relevant differences between inclisiran- and placebo-treated subjects; subjects with severe hepatic impairment have not been studied, which is reflected in the PI.

No safety concerns are evident in patients with impaired renal function, however, the number of subjects with severe renal impairment is too small for a conclusion. Non-clinical toxicology studies showed basophilic granules in the kidneys of rats and monkeys indicating accumulation of inclisiran but

these were not rated as adverse toxicological findings. Inclisiran should be used with caution in patients with severe renal impairment

## *3.6. Effects Table*

**Table 5.6.1:** Effects Table for HeFH (Study ORION-9) [n=482].

| Effect | Short Description | Unit | Inclisiran sodium 300 mg s.c. | PLC | Uncertainties/ Strength of evidence | Referen-ces |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| **LDL-C lowering** | % change from baseline in LDL-C to Day 510 | % | -41.15 | 8.37 | Effect estimate Inclisiran vs. Placebo:<br>-49.52<br>95% CI: -55.04,-43.99<br>p <0.0001<br>Supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.0001) | ORION-9 |
| | Time-adjusted % change in LDL-C from baseline after Day 90 up to Day 540 | % | -38.08 | 6.22 | Effect estimate Inclisiran vs. Placebo:<br>-44.30<br>95% CI: -48.48,-40.12<br>P <0.0001<br>Supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.0001) | ORION-9 |
| **CV risk lowering** | MACE (CV death, non-fatal MI, resuscitated cardiac arrest and nonfatal stroke) | % (n) | 4.1 (10) | 4.1 (10) | Not a prespecified efficacy endpoint | ORION-9 |
| **Unfavourable Effects** | | | | | | |
| **Injection site AEs** | | % | 8.2 | 1.8 | | Safety Pool phase III studies |
| **ALT >1x to 3x ULN** | Potentially clinically significant | % | 19.7 | 13.6 | | Safety Pool phase III studies |
| **AST >1x to 3x ULN** | Potentially clinically significant | % | 17.2 | 11.1 | | Safety Pool phase III studies |

Abbreviations: AE=adverse event, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, ULN=upper limit of normal
Notes: Safety data are from pooled analysis across all 3 pivotal phase III trials

**Table 5.6.2:** Effects Table for ASCVD (Study ORION-10) [n=1561].

| Effect | Short Description | Unit | Inclisiran 300 mg s.c. | PLC | Uncertainties/ Strength of evidence | Referen-ces |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| **LDL-C lowering** | % change from baseline in LDL-C to Day 510 | % | -56.34 | 1.30 | Effect estimate Inclisiran vs. Placebo:<br>-57.64<br>95% CI: -60.86,-54.43<br>p <0.0001<br>Supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.0001) | ORION-10 |
| | Time-adjusted % change in LDL-C from baseline after Day 90 up to Day 540 | % | -51.27 | 2.51 | Effect estimate Inclisiran vs. Placebo:<br>-53.78<br>95% CI: -56.23,-51.33<br>P <0.0001<br>Supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.0001) | ORION-10 |
| **CV risk lowering** | MACE (CV death, non-fatal MI, resuscitated cardiac arrest and nonfatal stroke) | % (n) | 7.4 (58) | 10.2 (79) | Not a prespecified efficacy endpoint | ORION-10 |
| **Unfavourable Effects** | | | | | | |
| **Injection site AEs** | | % | 8.2 | 1.8 | | Safety Pool phase III studies |
| **ALT >1x to 3x ULN** | Potentially clinically significant | % | 19.7 | 13.6 | | Safety Pool phase III studies |
| **AST >1x to 3x ULN** | Potentially clinically significant | % | 17.2 | 11.1 | | Safety Pool phase III studies |

Abbreviations: AE=adverse event, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, ULN=upper limit of normal
Notes: Safety data are from pooled analysis across all 3 pivotal phase III trials

**Table 5.6.3:** Effects Table for ASCVD or ASCVD-risk equivalents (Study ORION-11) [n=1617].

| Effect | Short Description | Unit | Inclisiran 300 mg s.c. | PLC | Uncertainties/ Strength of evidence | Referen-ces |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| **LDL-C lowering** | % change from baseline in LDL-C to Day 510 | % | -49.30 | 4.20 | Effect estimate Inclisiran vs. Placebo:<br>-53.50<br>95% CI: -56.66,-50.35<br>p <0.0001<br>Supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.0001) | ORION-11 |

| Effect | Short Description | Unit | Inclisiran 300 mg s.c. | PLC | Uncertainties/ Strength of evidence | Referen-ces |
|---|---|---|---|---|---|---|
| | Time-adjusted % change in LDL-C from baseline after Day 90 up to Day 540 | % | -46.58 | 3.35 | Effect estimate Inclisiran vs. Placebo:<br>-49.92<br>95% CI: -52.29,-47.55<br>P <0.0001<br>Supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.0001) | ORION-11 |
| **CV risk lowering** | MACE (CV death, non-fatal MI, resuscitated cardiac arrest and nonfatal stroke) | % (n) | 7.8 (63) | 10.3 (83) | Not a prespecified efficacy endpoint | ORION-11 |
| **Unfavourable Effects** | | | | | | |
| **Injection site AEs** | | % | 8.2 | 1.8 | | Safety Pool phase III studies |
| **ALT >1x to 3x ULN** | Potentially clinically significant | % | 19.7 | 13.6 | | Safety Pool phase III studies |
| **AST >1x to 3x ULN** | Potentially clinically significant | % | 17.2 | 11.1 | | Safety Pool phase III studies |

Abbreviations: AE=adverse event, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, ULN=upper limit of normal
Notes: Safety data are from pooled analysis across all 3 pivotal phase III trials

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Inclisiran used in patients with primary hypercholesterolaemia, mixed dyslipidaemia, and in patients with heterozygous familial hypercholesterolemia has demonstrated significant, consistent and clinically relevant reductions in LDL-C and other relevant lipid parameters like PCSK9, Total Cholesterol, ApoB, and non-HDL. The resulting effects on these lipid parameters were robust across several subgroups like age, gender, ethnicity, region, metabolic disease, baseline BMI, baseline LDL-C, intensity of statin treatment, non-statin lipid-lowering therapy, and baseline GFR category.

Lipid-lowering effects of inclisiran have been investigated in patients with and without co-administration of a statin. Therefore, the proposed indication is to use in patients on maximally tolerated statin therapy.

The lipid lowering effects of inclisiran are only a, albeit generally accepted, surrogate for beneficial effects on cardiovascular morbidity and mortality. Positive CV outcome studies are available for medicinal products with comparable effects, i.e. alirocumab and evolocumab. Analyses of MACE events for inclisiran on top of statins did exclude a trend towards cardiovascular harm, in line with the Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015). However, confirmation that the observed lipid-lowering effect will indeed result in improved cardiovascular outcome is still missing and needs to be addressed in the post-authorisation phase. Three long-term studies, including one CV outcome study are currently ongoing.

Long-term data of inclisiran on top of maximum tolerated statin therapy beyond 18 months of treatment can be considered limited, since the intended treatment may be lifelong. However, the data available indicate that efficacy is maintained over time and safety so far does not suggest any long-term major concerns.

The overall safety profile of inclisiran appears rather benign. AEs that were observed at a relevantly higher incidence with inclisiran compared to placebo were injection site reactions. These however were not associated with a higher dropout rate or a lower compliance. In fact, the dropout rate in the pivotal trials was low and comparable between groups and compliance in these trials was high. Furthermore, these injection site reactions might indicate hypersensitivity related to inclisiran, but no systemic allergic reactions or signs or symptoms suggestive of systemic allergic reactions were observed with the administration of inclisiran and TEAEs related to hypersensitivity did not indicate differences between groups except for events at the injection site. These adverse events were localised, predominantly mild or occasionally moderate, transient, and resolved without sequelae. No subject on inclisiran had a severe or serious injection site AE.

A higher frequency of mild to moderate ALT or AST elevations (> 1 x to 3 x ULN) were observed with inclisiran. However, no clinically meaningful changes (> 3 x ULN) in biochemical markers of hepatic function were identified in either group, the percentages of subjects with clinically relevant elevations of these markers were comparable between groups, and the percentages of subjects with AEs associated with hepatic safety were balanced between the placebo and the inclisiran group.

### 3.7.1. Balance of benefits and risks

Inclisiran is a first in class short interfering ribonucleic acid (siRNA) directed against PCSK9, which prevents the translation of PSCK9 and thus prevents LDLR degradation. This leads to clinically clearly meaningful LDL-C reduction.

The proposed indication for inclisiran is for use as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidaemia (including heterozygous familial hypercholesterolaemia) to reduce low-density lipoprotein cholesterol (LDL-C).

Patients participating in the 3 confirmatory studies were in need of further LDL-C lowering despite maximum tolerated statin therapy due to their increased cardiovascular risks. In the inclisiran treated patients, a substantial clinically relevant lipid reduction was observed with an acceptable safety profile. The safety findings currently do not indicate a significant risk associated with the use of inclisiran based on an extensive safety dataset with a treatment period of 18 months and low dropout rates. Data in patients with severe hepatic impairment are lacking and are very limited patients with severe renal impairment. Inclisiran should be used with caution in these patients.

The results of the 3 studies demonstrated a robust lipid-lowering in patients taking high intensity statins and in patients who were statin intolerant, even as there is no consensus definition for statin intolerance.

A limitation of the dossier is the lack of cardiovascular outcome data. Although a reduction in LDL-C is known to be a strong surrogate for cardiovascular risk reduction, this finding is mainly based on outcome data in numerous clinical studies obtained with statins. Also, recent studies with ezetimibe and PCSK9 inhibitors strengthen the value of LDL-C as a surrogate marker. As inclisiran has a new mode of action on LDL-C lowering, a similar relationship has to established. A cardiovascular outcome study is already ongoing and final results should provide confirmation of the expected cardiovascular benefit.

### *3.8. Conclusions*

The overall B/R of Leqvio is positive.

# 4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Leqvio is favourable in the following indication:

*Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:*

- *in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

### *Conditions or restrictions regarding supply and use*

Medicinal product subject to medical prescription.

### *Other conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

### *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new

information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## *New Active Substance Status*

Based on the CHMP review of the available data, the CHMP considers that inclisiran is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

## *Paediatric Data*

No significant studies in the agreed paediatric investigation plan P/0321/2018 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.