Title: Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

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None

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Rider on responsibility for report
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Please note that [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Acronym	Definition
ACS	Acute coronary syndrome
AE	Adverse events
ANCOVA	Analysis of covariance
Apo B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
ASCVD-RE	Atherosclerotic cardiovascular disease risk-equivalent
AUC	Area under curve
BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curve
CFB	% Change from baseline
CHD	Coronary heart disease
CI	Confidence interval
CODA	Convergence diagnostics and output analysis
CPRD	Clinical Practice Research Datalink
CrI	Credible interval
CS	Company submission
CSP	Clinical study protocol
CSR	Clinical study report
CTT	Cholesterol Treatment Trialists
CV	Cardiovascular
CVD	Cardiovascular disease
DB	Double blind
DIC	Deviation information criterion
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
EQ-5D	EuroQol five dimensions
ERG	Evidence review group
ESC	European Society of Cardiology
FE	Fixed-effects
FH	Familial hypercholesterolaemia
GP	General practitioner
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HES	Hospital episode statistics
HoFH	Homozygous familial hypercholesterolaemia
HRQoL	Health-related quality of life
hsCRP	High sensitivity C-reactive protein
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
IP	Investigational product
IS	Ischaemic stroke
ITC	Indirect treatment comparison
ITT	Intention to treat

Acronym	Definition
JAS	Japan atherosclerosis society
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein-cholesterol
LLT	Lipid lowering therapy
LMTs	Lipid-modifying treatments
Lp	Lipoprotein
LSM	Least squares mean
MACE	Major adverse cardiac event
MI	Myocardial infarction
MMRM	Mixed-effect models for repeated measures
MTD	Maximally tolerated dose
NA	Not applicable
NCEP-ATP	National cholesterol education program-adult treatment panel III goal
NF	Non-fatal
NF-MI	Non-fatal myocardial infraction
NF-stroke	Non-fatal stroke
NHS	National health system
NICE	The National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NYHA	New York Heart Association
OD	Oral daily
ONS	Office of national statistics
OR	Odds ratio
PAD	Peripheral arterial disease
PAS	Patient access scheme
PC	Placebo-controlled
PCSK9	Proprotein convertase subtilisin/kexin type 9
PICOS	Population, intervention, comparator, outcome, study design
PMM	Pattern mixture model
PPER	Primary prevention with elevated risk
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSS	Personal social service
QALY	Quality-adjusted life year
QALYs	Quality adjusted life years
RCT	Randomised controlled trial
RE	Risk equivalent
Revasc	Revascularization
RoB	Risk of bias
ROBIS	Risk of Bias in Systematic reviews tool
RR	Rate ratio
SA	Sensitivity analyses
SAE	Serious adverse events
SAMS	Statin-associated muscle symptoms
SAS	Statistical analysis set
SC	Subcutaneous
SLR	Systematic literature review

Acronym	Definition
SoC	Standard of care
SR	Systematic review
STA	Single technology appraisal
SUCRA	Surface under the cumulative ranking area
T2D	Type 2 diabetes
TC	Total cholesterol
TEAE	Treatment emergent adverse event
TESAE	Treatment-emergent serious adverse event
TRAE	
UA	Unstable angina
UK	United Kingdom
VLDL-C	Very-low-density lipoprotein-cholesterol
WTP	Willingness-to-pay

Table of Contents

List of Tables

List of Figures

Key issues for Technical Engagement

Common key issues: decision problem

The intervention matches the scope. The population is narrower than the population in the NICE scope. The population was divided into *a) secondary prevention population* (adults with Atherosclerotic Cardiovascular Disease [ASCVD]) and b) *primary prevention populations* (primary prevention population with elevated risk [PPER] and c) *adults with a history of heterozygous familial hypercholesterolaemia [HeFH]).* The population is narrower than the marketing authorisation as only hypercholesterolaemia patients with a serum LDL-C of ≥2.6mmol/L are considered. The company have sought to align the population in the submission with that [redacted] The comparators listed differ from the NICE final scope and ezetamibie was better placed as an active comparator. The outcomes are similar to the scope except for the removal of apheresis which is appropriate.

Common key issues: clinical effectiveness evidence

- Use of the [redacted] threshold is supported by existing trial data and are supported by the [redacted] and does not address the full scope of the decision problem.
- The ERG noted that a lack of genetic testing for all suspected FH cases may result in cases either being missed or being classified into other population groups (e.g. PPER or ASCVD).
- Ezetimibe would have been an appropriate active comparator rather than standard of care.
- Only ORION-11 recruited patients from the UK; 462 patients from 23 sites which may compromise the generalisability of the results.
- The ERG believes that the evidence of agreement between the direct and indirect estimates from closed loops provided by the company gives an additional assurance that the transitivity assumption was not gravely violated and that the effect modifiers were not distributed differentially across the network comparisons.

- The ERG does not agree with company assumption that for the base-case analyses differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) would not impact the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations. The ERG considers the company's assumptions and recommendations regarding the handling of effect modifiers and the steps taken in sensitivity analysis to be relevant and adequate in light of the available evidence and its limitations.

- To address the unclear and high risk of bias identified for GAUSS-4, this study was removed from the NMA. This analysis produced similar results.

Common key issues: cost-effectiveness evidence

- Ezetimibe is not included by the company as an active comparator within model, as outlined in the NICE final scope, but was included as part of SoC for all populations modelled.

- The ERG identified many technical errors within both the original and updated models provided by the company. This limited the ability of the ERG to validate the results of scenario analyses and PSA provided and to undertake additional scenario and sensitivity analyses.

- The ERG note use of Mohrschladt et al.[1] data as the source of CV event rates for the secondary prevention HeFH population in the company's subgroup analysis. This was justified by its use in previous TA393[2] despite more recent data available. Technical errors in the model prohibited the ERG conducting scenario analyses with alternative data sources to establish the impact on the base-case ICER.

Executive summary

Overview of the ERG's key issues

- Ezetimibe would have been an appropriate active comparator rather than positioning it under standard of care in the CS decision problem. Ezetimibe not included by the company as an active comparator within model, as outlined in the NICE final scope, but was included as part of SoC for all populations modelled.

- The ERG identified many technical errors within both the original and updated models provided by the company. This limited the ability of the ERG to validate the results of scenario analyses and PSA provided and to undertake additional scenario and sensitivity analyses.

- The ERG does not agree with company assumption that for the base-case analyses differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) would not impact the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations. The ERG considers the company's assumptions and recommendations regarding the handling of effect modifiers and the steps taken in sensitivity analysis to be relevant and adequate in light of the available evidence and its limitations.

- The ERG note use of Mohrschladt et al.[1] data as the source of CV event rates for the secondary prevention HeFH population in the company's subgroup analysis. This was justified by its use in previous TA393[2] despite more recent data available. Technical errors in the model prohibited the ERG conducting scenario analyses with alternative data sources to establish the impact on base-case ICER.

Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. Where a small reduction in QALYs is seen with a substantial decrease in costs, value can be represented by cost savings achieved through QALYs forgone.

- Overall, in the primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia population, the effect of inclisiran on QALY yield is:

- An increase in QALYs gained, due to reduction in disutilities sustained through CV events, when compared with SoC.
- Fewer QALYs gained, due to increased disutilities sustained through CV events, when compared with alirocumab and evolocumab.
- No change in QALYs against any comparator through adverse event disutilities, which were not included within the model.

- Overall, in the primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia population, inclisiran is modelled to affect costs by:
  - Lower unit price (than other lipid lowering therapies (LLT) at list price).
  - Higher administration costs (than other lipid lowering therapies (LLT) at list price).
  - Higher post-CV event health state management costs than alirocumab and evolocumab at list price.
  - No difference in adverse event costs which were not included in the model when compared with other lipid lowering therapies (LLT).

The decision problem: summary of the ERG's key issues

- The population is narrower than the population in the NICE scope and the marketing authorisation. The population was divided into *a) secondary prevention population* (adults with Atherosclerotic Cardiovascular Disease [ASCVD]) and b) *primary prevention populations* (primary prevention population with elevated risk [PPER] and c) *adults with a history of heterozygous familial hypercholesterolaemia [HeFH]).* The company have sought to align the population in the submission with that [redacted]
- The comparators listed differ from the NICE final scope and ezetamibie was better placed as an active comparator. The outcomes are similar to the scope except for the removal of apheresis which is appropriate.

The clinical effectiveness evidence: summary of the ERG's key issues

- Evidence for the clinical effectiveness of inclisiran comes from three RCTs: ORION-9, ORION-10 and ORION-11, which were Phase III, randomised, double-blind, placebo-controlled trials. The objectives of the ORION trials were to assess the

efficacy, safety, and adverse-event profile of inclisiran over a period of 18 months in patients at high risk for cardiovascular disease in whom LDL cholesterol levels were elevated despite receiving statin therapy at the maximum tolerated dose with or without additional lipid-lowering therapy.

- Inclusion criteria in the ORION trails were mostly identical except for disease history and serum LDL levels to reflect the indications in each trial.
- Overall, treatment with inclisiran resulted in statistically significant decreases in LDL-C levels (mean percentage change in LDL-C and the time-adjusted percentage change) across all three ORION trials for both co-primary endpoints.
- The company provided an indirect treatment comparison of thirty-nine eligible RCTs evaluating the efficacy and safety of inclisiran as well as specific treatment comparators (i.e., alirocumab, evolocumab, ezetimibe, and placebo) along with outcomes of interest.
- The ERG notes that the treatment nodes were connected correctly in the three NMA plots. The ERG considers the company's overall approach for assessing the feasibility of NMA to be appropriate, as it conforms the existing NMA recommendations.
- ORION-10 and ORION-11 were pooled in the NMA based on the similarity between baseline characteristics, LDL-C levels and overall methodology. Sensitivity analyses wherein ORION-10 and ORION-11 were not pooled (i.e. separate analyses were conducted based on each inclisiran trial) would have been informative.
- High statistical heterogeneity was observed in the NMA comparing alirocumab and placebo in the HeFH population. ODYSSEY HIGH FH had the highest mean baseline LDL-C compared to the other studies in this network and was therefore excluded in a sensitivity analysis which resulted in findings that were consistent with the base case in terms of direction of effect and statistical significance.
- The ERG does not agree with company assumption that for the base-case analyses differences in CV risk and severity of patients within each population strata of interest would not impact the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations. The ERG considers the company's assumptions and recommendations regarding the handling of effect modifiers and the steps taken in sensitivity analysis to be relevant and adequate in light of the available evidence and its limitations.

- Studies used inconsistent definitions and criteria for categorizing CV risk. These inconsistencies coupled with poor reporting (e.g., for many studies proportion of people intolerant to statins, ASCVD, CHD, PPER were not reported) is a limitation of the evidence which complicates assessment of the impact of CV risk on treatment efficacy, and may have compromised the assumption of transitivity.

The cost-effectiveness evidence: summary of the ERG's key issues

The ERG identified the key issue with the company's cost-effectiveness evidence as the inclusion of ezetimibe as part of SoC across all populations. Details are summarised in the following issues table.

Issue 1: Inclusion of ezetimibe as part of SoC rather than as active comparator

Report section	**Section 3.2.7**
Description of issue and why the ERG has identified it as important	Inclusion of ezetimibe as SoC (in addition to maximally tolerated statins) rather than as active comparator in deviation from NICE final scope. Ezetimibe inhabits the same position in the treatment pathway of hypercholesterolaemia as inclisiran is seeking marketing authorisation from and is therefore an active comparator, not just part of SoC. This will likely have significant effect on the ICER for inclisiran, as now ezetimibe is available in generic form (since 2017/18), its cost effectiveness has increased.
What alternative approach has the ERG suggested?	Ezetimibe treated as an active comparator, not as part of SoC, in the base case.
What is the expected effect on the cost-effectiveness estimates?	In the ASCVD population the ezetimibe & SoC dominated SoC alone and increased the ICER for inclisiran and SoC to [redacted] In the PPER population the ezetimibe & SoC dominated SoC alone and increased the ICER for Inclisiran and SoC to [redacted] The ICERs for each population presented are effectively doubled in this scenario.
What additional evidence or analyses might help to resolve this key issue?	The same analysis to be conducted in the primary HeFH population as the company state it was not possible to include ezetimibe in the NMA for this population. The ERG accept that efficacy data for ezetimibe in this population may not be available in the literature to facilitate this analysis.

The ERG identified multiple technical errors in the company's model when attempting to run PSAs for the ASCVD and PPER populations. Further assessment of how robust these ICERs are to changes in input parameters was therefore not possible.

Other key issues: summary of the ERG's view

The ERG identified many technical errors within both the original and updated models provided by the company. This limited the ability of the ERG to validate the results of scenario analyses and PSA provided and to undertake additional scenario and sensitivity analyses.

The ERG note use of Mohrschladt et al. data as the source of CV event rates for the secondary prevention HeFH population in the company's subgroup analysis. This was justified by its use in previous TA393 despite more recent data available. Technical errors in the model prohibited the ERG conducting scenario analyses with alternative data sources to establish the effect on the ICER using up-to-date event rates in this subgroup.

Summary of ERG's preferred assumptions and resulting ICER

The ERG outline their preferred assumption below. In Table 1 we provide numerical estimates of the resulting ICER(s) in a fully incremental analysis and indicate the change from the company's base case ICER(s) to ERG base-case ICER(s).

Table 1. Summary and impact of each change on the company's base-case ICERs

Population and scenario	ICER (£/QALY)	Change from base-case (%)
ASCVD		
Company' base-case	[redacted]	[redacted]
Inclusion of ezetimibe as an active comparator	[redacted]	[redacted]
PPER		
Company's base-case	[redacted]	-
Inclusion of ezetimibe as an active comparator	[redacted]	[redacted]
Primary prevention HeFH		
Company's base-case	[redacted]	[redacted]
Inclusion of ezetimibe as an active comparator	Analyses was not undertaken due to the paucity of information.	

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

This single technology appraisal (STA) concerns the use of inclisiran, alone or with a statin, with or without other lipid-lowering therapy for treating people with primary hypercholesterolaemia or mixed dyslipidaemia.

1.2 Disease overview

Hypercholesterolaemia is defined as the presence of increased levels of cholesterol (primarily low-density lipoprotein; LDL-C) in the blood,[3] while the term “mixed dyslipidaemia” is used to describe a combination of increased levels of LDL-C and triglyceride levels, and decreased high-density lipoprotein (HDL-C).[4] About 50% of UK adults live with cholesterol levels exceeding national guideline recommendations (total cholesterol >5 mmol/L).[4]

Lipoproteins are aggregates of lipids and proteins that are usually found circulating in the bloodstream. They transport lipids, mainly cholesterol and triglycerides, to the cells and tissues of the body. Excessive levels of non-HDL-C and/or LDL-C lead to a build-up of fatty material (plaques or atheroma) on the walls of arteries - a process called atherosclerosis.[5, 6] Consequently, there is hardening and narrowing of the arteries thereby restricting blood flow and oxygen supply to vital organs, increasing the risk of blood clot formation.

Low density lipoprotein (LDL-C) is known to be a major causal risk factor for Atherosclerotic cardiovascular disease (ASCVD).[6] Moreover, there is a “dose-dependent” association between exposure to LDL-C and the risk of ASCVD, whereby the risk of ASCVD increases with increasing duration of exposure to LDL-C. About 4.7 million individuals live with ASCVD in the UK, this figure is expected to increase because of the ageing population and improved survival following CV events.[4] Meanwhile about 1.1 million adults in England have ASCVD and LDL-C levels ≥2.6 mmol/L, despite receiving statins and/or ezetimibe (CS Document B, section B1.3.3.2, page 31).

1.2.1 Familial and non-familial hypercholesterolaemia

Broadly, there are two forms of hypercholesterolaemia: familial and non-familial disease. Familial hypercholesterolaemia (FH) is inherited following an autosomal dominant pattern with most people manifesting the heterozygous form (HeFH). Familial hypercholesterolaemia (FH) predisposes to early-onset myocardial infarctions (MI), even as early as the third decade of life.[7] People with FH may belong to a primary prevention population with elevated

risk (PPER - those who have not yet experienced a CV event but are at elevated risk of an event due to their FH) or a secondary prevention population (those that have already experienced an ASCVD event). Familial hypercholesterolaemia (FH) affects about 1 in 311 people.[8] It is estimated that 38,000 individuals in England have FH and an LDL-C level ≥2.6 mmol/L, despite receiving statins and/or ezetimibe.[8] About 8.2 million individuals in the UK may be at increased risk of developing ASCVD out of which about 5.3 million are receiving lipid-lowering therapies.

Non-familial hypercholesterolaemia (non-FH) has no specific genetic cause. Rather it is usually multifactorial.[9]

Patients with FH but no other major risk factors who are yet to experience an event - the 'FH primary prevention patients' - are considered 'high risk' or 'very high risk' according to ESC/EAS guidelines.[10] Some FH patients may go on to experience an event and therefore become categorised as ASCVD patients, resulting in a clinical overlap. However, they remain inherently considered as 'secondary prevention FH patients.

1.3 Background

1.3.1 Critique of company's overview of current treatment pathway

Generally, the ERG found the company's description of the current treatment pathway to be accurate but disagree on the positioning of ezetimibe in Figure 3 (CS Document B, Section B.1.5.3, page 36). According to NICE, ezetimibe can be used for treating both primary-heterozygous familial (HeFH) and non-familial hypercholesterolaemia with statin therapy or if statin is not tolerated,[11] this suggests that there are varying profiles of patients that are prescribed ezetimibe. For example, while some patients will be prescribed ezetimibe because they cannot tolerate the maximum dose of statins, some other patients will receive ezetimibe as add-on to statins. The ERG clinical advisor agree with the positioning of ezetimibe after statin therapy This may create some difficulty in understanding how best to assess the comparative efficacy or effectiveness of ezetimibe versus inclisiran. However, the key trials (ORION 9, ORION 10, ORION 11) underpinning the current appraisal compared inclisiran versus placebo.

1.3.2 Critique of the company's proposed place of the technology in the treatment pathway

The company proposed the use of inclisiran 'if maximally tolerated dose of statin with or without ezetimibe does not result in LDL-C goals being reached or if statin is contraindicated

or not tolerated' (CS Document B, Section B.1.3.5, page 35). However, both the ERG and the ERGs clinical advisor believe that ezetimibe should serve as a comparator to the technology rather than "standard of care/usual care".

1.4 *Critique of company's definition of decision problem*

The ERG provide a comparison of the NICE final scope and CS decision problem in Table 2 of this report.

1.4.1 Population

The CS population (CS Table 1, p17) is narrower than the population in the NICE scope and the expected marketing authorisation for inclisiran. Both the final NICE scope and current marketing authorisation list "*people with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia"*.[12] The CS population (CS Table 1, p17) is narrower than the population in the NICE scope and the expected marketing authorisation for inclisiran. Both the final NICE scope and current marketing authorisation list "*people with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia"*.[12]

In the CS decision problem the population has been divided into a secondary prevention population (adults with Atherosclerotic Cardiovascular Disease [ASCVD]) and two primary prevention populations (primary prevention population with elevated risk [PPER] and adults with a history of heterozygous familial hypercholesterolaemia [HeFH]). The ERG sought clarification as to how those with heterozygous mutations would be determined. The company's response clarified that *in current practice some but not all patients will receive genetic testing. Familial hypercholesterolaemia is only expected in those with very high total cholesterol (>7.5 mmol/L) and with a family history. HeFH is confirmed by either genetic testing or the use of existing criteria (Simon Broome criteria or Dutch Lipid Clinic Network).* [13] The ERG noted that a lack of genetic testing for all suspected FH cases may result in cases either being missed or being classified into other population groups (E.g. PPER or ASCVD).

The company added the phrase "despite maximally tolerated statins" as a population criterion. The phrase "maximally tolerated statins" here is used to include those in whom statins are contraindicated or not tolerated. The company defines the phrase, as the maximum regular dosage that can be taken without any adverse events occurring, mirroring the phrasing from the ORION trial protocols.

The population presented in this submission is narrower than the marketing authorisation as only hypercholesterolaemia patients with a serum LDL-C of ≥2.6mmol/L are considered.[12] The company have sought to align the population in the submission with that [redacted]

There were several justifications for the addition of this threshold. Firstly, the lowest reported baseline mean serum LDL-C was 2.7mmol/L in the ORION trials (inclisiran arm ORION 10 and placebo arms ORION 10 and 11; CS B.2.3.6 p60, table 12). Secondly, in the ODYSSEY trial for alirocumab a greater clinical reduction was observed in those with baseline LDL-C ≥2.6 mmol/L (CS B.1.3.5).[14] The ERG agrees, despite the differences in trial design between the ORION and ODYSSEY trials, there were comparable similarities in baseline characteristics of the populations, and as no statistically significant differences were found between inclisiran and alirocumab in the CS NMA (2.3.2.1), the two treatments were similarly effective in this population. Furthermore, the ERG clinical advisor agreed the threshold of 2.6 mmol/L is suitable for two populations (adults with ASCVD despite maximally tolerated statins and adults with history of HeFH without ASCVD despite maximally tolerated statins).

Whilst these arguments support the use of ≥2.6 mmol/L as a clinically effective threshold, they do not account for the complete population falling under the marketing authorisation of inclisiran. For example, patients with an LDL-C <2.6mmol/L may need to reduce LDL-C further to achieve target treatment levels (for high risk <1.8 mmol/L and very high risk <1.4 mmol/L as outlined in ESC/EAS guidelines[10]). Likewise, primary HeFH patients with LDL-C <2.6mmol/L who need to reduce to minimum achievable levels would also be missed.

In summary, the ERG find:

The distinctions of the populations appropriate within this submission. However, there are some concerns that without genetic testing some HeFH cases will be missed.

Use of the [redacted] threshold is supported by existing trial data and are supported by the [redacted] and does not address the full scope of the decision problem.

1.4.2 Intervention

The intervention listed in the company decision problem matches that in the NICE final scope: inclisiran alone or with a statin, with or without other lipid-lowering therapy.

1.4.3 Comparators

The comparators listed in the CS decision problem differ from the NICE final scope.

As bempedoic acid was subject to an ongoing NICE appraisal at the time the CS wrote their decision problem, they excluded it as a comparator. The ERG agrees with this rationale, consolation end date is expected on the 11th of January 2021. However, the ERG notes:

Bempedoic acid, with or without fixed dose ezetimibe (available as a combined tablet), is orally administered, whereas inclisiran is injected.

The manufacturers are also seeking marketing authorisation in the UK for treating primary hypercholesterolaemia or mixed dyslipidaemia and the proposed position in the clinical treatment pathway of bempedoic acid (+/- fixed dose ezetimibe) is the same as inclisiran.

This suggests that bempedoic acid is potentially an extremely pertinent comparator to inclisiran. The GID-TA10534 appraisal is currently ongoing. Project updates are provided on NICE's website. The ERG note that if bempedoic acid were to be approved by NICE, whilst not part of established clinical practice, the availability of another treatment option in the primary care pathway with an alternative route of administration may prove significant in both prescription and uptake of inclisiran.

The CS decision problem includes ezetimibe in all arms, reporting it as a current standard of care (SoC). The ERG sought clarification regarding adding ezetimibe as SoC as the company cite it's infrequent use ((4.1% in ASCVD, 1.5% in PPER, 5.4% in HeFH); (Appendix L, CS submission) and limited potency compared to other lipid lowering alternatives (20%, CS B.1.3.6.3). In support of adding ezetimibe as SoC the CS refer to clinician input. However, the response

[redacted]

The reason for this decision being

[redacted]

The ERG agrees with the company that depending on the individual patient, ezetimibe can be used in the UK for patients in whom statins are contraindicated. At the same time, it can be regarded as an active comparator given that there are patients receiving statins who also receive ezetimibe (CS section B.2.3.6, table 12, 436/482 patients in ORION-9 received statins and 255/482 patients also received ezetimibe). The ERG clinical advisor clarified that in practice ezetimibe is after/with statins, following dietary treatment then statins (or in place of statins if the patient is intolerant). This would place it as a comparator to inclisiran. The ERG is aware of the potential to review and update NICE appraisal of Ezetimibe (TA385) (see pg. 149 Section 3.3.7 for further details).

However, it is the opinion of the ERG that it would have been more useful to see data on ezetimibe as an active comparator.

In summary, the ERG find:

The exclusion of bempedoic acid as a comparator appropriate given the ongoing NICE appraisal. Ezetimibe would have been an appropriate active comparator.

1.4.4 Outcomes

The CS decision problem has removed apheresis as an outcome with the justification that this is usually prescribed for homozygous familial hypercholesterolaemia, not HeFH. For HeFH, which is of interest in this review, it is very infrequently used. The company refer to NICE guidance TA394 which recommends the use of apheresis on those with severe HeFH, but noted that within the guidance apheresis for HeFH is “not only costly and onerous for the patient but also difficult to access because only a few centres offer it”.[15] The company estimate current use of apheresis to be less than 0.05% of the ASCVD and primary prevention population. The company base this estimate upon current apheresis services treating 1,200 patients per year, including adults, children and other illnesses for which the treatment would be appropriate.[16] The ERG clinical advisor agreed that it is extremely rare for apheresis to be offered for those with HeFH or ASCVD in practice.

The ERG agree the exclusion of apheresis as an outcome to be appropriate.

1.4.5 Other relevant factors

The CS followed a different subgroup analysis to the NICE scope. Instead of considering presence or risk of CVD, HeFH, people with statin intolerance and severity of hypercholesterolaemia, the CS has stratified based upon three populations – ASCVD, PPER and HeFH without ASCVD, with further analysis of these groups by severity of

hypercholesterolaemia, presence of HeFH for patients with ASCVD and statin intolerance. The company analysed severity by using serum LDL-C thresholds of ≥4.0 mmol/L and ≥3.5mmol/L in those who are very high risk, and a threshold of >5.0 mmol/L for those with HeFH without CVD. These thresholds were determined based upon existing NICE recommendations for alirocumab and evolocumab.[2, 15]

The ERG finds these thresholds appropriate based upon current NICE guidance.

Table 2: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia	Secondary prevention population • Adults with ASCVD (including HeFH) and serum LDL-C ≥2.6 mmol/L despite maximally tolerated statins Primary prevention population • Adults who are primary prevention with elevated risk	The population described in the final scope broadly captures the anticipated licensed indication for inclisiran. However, the population addressed in this submission is narrower than the marketing authorisation to reflect the available clinical evidence. Current recommendations are different for patients with non-familial and familial hypercholesterolaemia, and patient characteristics also differ between these populations. In clinical trials, greater absolute risk reduction is observed in patients with baseline LDL-C ≥2.6 mmol/L than those with lower baseline levels.[14] Therefore, inclisiran is expected to provide the greatest clinical benefit in this population. This threshold has historically been	The population in the CS decision problem is restricted to those with baseline serum LDL-C ≥2.6 mmol/L despite maximally tolerated statins. This threshold is supported by evidence from existing trials, but not reflected in the current marketing authorisation.[12]

		(PPER*) with serum LDL-C≥2.6 mmol/L despite maximally tolerated statins • Adults with a history of HeFH without ASCVD and serum LDL-C ≥2.6 mmol/L despite maximally tolerated statins. The primary prevention populations are non-mutually exclusive; the PPER population is a broader group	considered a threshold for up-titration and add-on therapy for PCSK9 inhibitors,[18] and is approximately aligned with the mean baseline LDL-C levels observed in the ORION-10 and ORION-11 trials (Section B.2.3.6 CS). [redacted]	

		encompassing people who are at elevated risk for a range of reasons (potentially including HeFH), while the HeFH group are at elevated risk specifically due to HeFH. *Note that in the ORION-10/-11 trial publication and the clinical trial write-up in Section B.2, primary prevention patients with elevated risk are referred to as 'ASCVD risk-equivalents'.[17] This term is synonymous with the term 'primary prevention with elevated risk' used elsewhere in this dossier.		

Intervention	Inclisiran, alone or with a statin, with or without other lipid-lowering therapy	As per final scope	Not applicable	The intervention in the CS matches the NICE final scope.
Comparator(s)	• Maximally tolerated statins • When statins are contraindicated or not tolerated: o Ezetimibe o Evolocumab (with or without another lipid-lowering therapy) o Alirocumab (with or without another lipid-lowering therapy) • When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C: o Ezetimibe (when evolocumab and alirocumab are not appropriate) o Evolocumab (with or without another lipid-lowering therapy)	• SoC, comprising of maximally tolerated statins with or without ezetimibe • When maximally tolerated statin dose does not appropriately control LDL-C: o SoC, comprising of maximally tolerated statins with or without ezetimibe o Evolocumab with a statin (with or without another lipid-lowering	Ezetimibe is included as part of SoC and therefore as part of background therapy in all arms. This is based on clinician input (20), and the infrequent use of ezetimibe in clinical practice (4.1% in ASCVD, 1.5% in PPER, 5.4% in HeFH; (Appendix L). Clinical experts' feedback has also suggested that with the addition of ezetimibe to a statin, whilst patients do achieve some reduction in their LDL-C level, it is counter-productive as this reduction in LDL-C prevents patients from being eligible for more advanced therapies that are likely to offer a greater reduction. Bempedoic acid is not considered as a comparator as it is subject to an ongoing NICE	The ERG agrees with the removal of bempedoic acid as a comparator given the ongoing NICE appraisal. [redacted]. Particularly, given it's rare use in clinical practice. The ERG advisor confirmed the placement of ezetimibe in the clinical pathway following dietary management and statins, placing it in the same position in the clinical pathway as inclisiran. It can be used as an active comparator for patients.

	o Alirocumab (with or without another lipid-lowering therapy) o Bempedoic acid (subject to ongoing NICE appraisal). • When maximally tolerated does not appropriately control LDL-C: o Ezetimibe with a statin o Evolocumab with a statin (with or without another lipid-lowering therapy) o Alirocumab with a statin (with or without another lipid-lowering therapy) • When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C: o Ezetimibe with a statin (when evolocumab and alirocumab are not	therapy) o Alirocumab with a statin (with or without another lipid-lowering therapy) • When statins are contraindicated or not tolerated: o SoC, comprising alternatives to statins e.g. ezetimibe, other lipid-lowering therapy or no treatment o Evolocumab (with or without another lipid-lowering therapy) o	appraisal and therefore cannot be considered part of established clinical practice.	

	appropriate) o Evolocumab with a statin (with or without another lipid- lowering therapy) o Alirocumab with a statin (with or without another lipid-lowering therapy) o Bempedoic acid with a statin (subject to ongoing NICE appraisal)	Alirocumab (with or without another lipid-lowering therapy)		

Outcomes	The outcome measures to be considered include: • plasma lipid and lipoprotein levels, including LDL-C, non-HDL-C, apolipoprotein B and lipoprotein-a • requirement of procedures including LDL apheresis and revascularisation • fatal and non-fatal cardiovascular events • mortality • adverse effects of treatment • health-related quality of life.	As per final scope, except for apheresis	The outcomes specified in the final scope are broadly appropriate. However, apheresis is generally prescribed for HoFH, which is not part of the anticipated indication for inclisiran, and is used very infrequently for HeFH in England. The committee in TA394 were aware that "although apheresis is recommended in the NICE guideline on familial hypercholesterolaemia as an option for severe heterozygous-familial hypercholesterolaemia, it is not only costly and onerous for the patient, but also difficult to access because only a few centres offer it".[15]	The outcomes in the CS match those in the NICE scope, except for apheresis. Based on current NICE guidelines and the lack of uptake in general for apheresis in the UK, the ERG agrees it was appropriate to remove this as a comparator.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			

Subgroups	If the evidence allows the following subgroups will be considered: • presence or risk of CVD • people with HeFH • people with statin intolerance • severity of hypercholesterolaemia.	Stratification based on: • Adults with a history of ASCVD o with HeFH o serum LDL-C ≥4.0 mmol/L o serum LDL-C ≥3.5 mmol/L and who are very high risk o statin intolerance • primary prevention for those with elevated risk o statin intolerance • primary prevention for adults with HeFH o serum LDL-C ≥4.0 mmol/L o serum	The subgroups specified in the final scope are broadly appropriate. However, the three populations (ASCVD, PPER and HeFH without ASCVD) will be considered separately in the model and will be further stratified by severity of hypercholesterolaemia, presence of HeFH for patients with ASCVD and statin intolerance. Levels of severity are defined based on current NICE recommendations for alirocumab and evolocumab.[2, 15] We propose to model statin contraindication/intolerance as a subgroup, since maximally tolerated statin dose incorporates patients that do not tolerate statins. In the main analysis, the patient characteristics, risks, and background therapies received will reflect the combined characteristics of people who are tolerant and intolerant of statins as a weighted average, as represented in the ORION	The thresholds the company have used in the subgroup analysis, mirror the current NICE guidelines in place for alirocumab and evolocumab.[2, 15] The ERG feels the subgroup analyses undertaken were appropriate.

		LDL-C ≥5.0 mmol/L o statin intolerance	clinical trial programme, across which [redacted] of ASCVD patients were statin intolerant (The Medicines Company - Summary of Clinical Efficacy 2.7.3 Data on file [INC-DOF-003] document provided with the CS).	
Special considerations including issues related to equity or equality	NR Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	NR in the decision problem however in their write up the company state that CVD is one of the health conditions most strongly associated with health inequalities, particularly in secondary care. Inclisiran will be delivered in primary care to reduce outpatient and secondary care burden.	NR	While the ERG agree that the use of inclisiran will reduce some of the existing health inequalities, there are many other CVD related outcomes not linked to LDL-C levels which inclisiran may not target which will remain a problem in secondary care. For example non-HDL-C can also predispose to CVD-related outcomes. Current marketing authorisation reflects the original NICE scope, as opposed to the narrower populations and thresholds the company has imposed.

2 CLINICAL EFFECTIVENESS

2.1 *Critique of the methods of review(s)*

The CS presents a systematic review (SR) that aimed to answer the following research question: "What is the comparative efficacy and safety of inclisiran versus other pharmacologic agents for the management of hypercholesterolaemia (heterozygous familial and non-familial) and 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 in patients who are statin-intolerant, or for whom a statin is contraindicated?" (CS appendix D, page 1).

The ERG critique of the SLR is provided below. The review processes were described for study selection (methods and number of reviewers) and for data extraction but not in much detail. There was evidence that suboptimal processes were employed (e.g. same single reviewer data extraction with checking) and the methods described in the CS submission were followed. Table 3 provides the ERG quality assessment of the CS clinical effectiveness SLR.

Overall, ***the ERG considers the chance of systematic error in the clinical effectiveness SLR to be low.***

Table 3: ERG assessment of risks of bias of the CS systematic review of clinical effectiveness

ROBIS domain, and signalling questions	ERG's assessment of whether criteria met, with comments
1: Study eligibility criteria	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably yes**. In appendix D the company refer to the protocol although no document has been provided and does not appear to have been published. Eligibility criteria are defined in table 6, appendix D. Retrospective criteria were added to remove bempedoic acid and icosapent ethyl as comparators . The ERG deems this appropriate given that icosapent ethyl is not listed on the NICE scope as a comparator and there is an ongoing NICE appraisal review being undertaken on bempedoic acid use for hypercholesterolaemia. The company also retrospectively applied a cut off date of 2015 to systematic reviews. A further criteria was added but not reported which was to exclude abstracts prior to 2018.
1.2 Were the eligibility criteria appropriate for the review question?	**Yes**. Objective of the submission is to evaluate inclisiran for people with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia. All areas were covered within the criteria reported.
1.3 Were eligibility criteria unambiguous?	**Yes.** All eligibility criteria clear in table 6, appendix D. Further notes provided to specify the criteria regarding statin use and the criteria for low intensity.
1.4 Were all restrictions in	**Yes.** Restrictions were applied to the population,

eligibility criteria based on study characteristics appropriate?	interventions, comparators, study design and publication type. The ERG deemed All restrictions appropriate.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Probably yes.** Information regarding the publication status and format is provided, and studies were excluded for not reporting on outcomes of interest. No information is provided as to whether language was considered an exclusion criterion.
Domain 1 risk of bias	**Low**
2: Identification and selection of studies	
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**. Searches were conducted in an appropriate set of bibliographic databases (MEDLINE, MEDLINE In-Process, Embase, Cochrane Library).
2.2 Were methods additional to database searching used to identify relevant reports?	**Yes**. Supplementary searches of conferences (published in 2018 and onwards) and two clinical trial registers were conducted as well as hand searching referencing lists of clinical practice guidelines, systematic literature reviews and relevant studies identified. Handsearching was undertaken of HTA body websites and clinical study reports.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably yes**. Detailed search strategy provided (CS Appendix D, Tables 1 – 3). Suitable terms for the condition, treatment and study types were included and combined appropriately. Terms for NICE comparators plus an additional treatment were included, but terms for statins were not.
2.4 Were restrictions based on date, publication format, or language appropriate?	**Yes**. A retrospective date limit was applied to the systematic reviews only. The company included earlier publications meeting the inclusion criteria identified by reviewing the references and included studies and systematic review found in their searches. The restrictions applied to publication format were appropriate. No information has been provided as to whether any language restrictions were included.
2.5 Were efforts made to minimise errors in selection of studies?	**Yes.** Appropriate assessment of titles and abstracts and full texts by two independent reviewers, with disputes between reviewers referred to a third reviewer. The PICO and reasons for exclusion are clearly presented.
Domain 2 risk of bias	**Low**
3: Data collection and study appraisal	
3.1 Were efforts made to minimise error in data collection?	**Probably yes**. Data extraction undertaken by two independent reviewers, which was later changed to full extraction by one reviewer with second reviewer checking. No information provided on any templates used for extraction.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	**Yes**. Extensive information present about the three ORION trials in the CS (CS submission Pages 46 – 114 and Appendix D,). Information extracted for the comparator studies identified by the systematic literature review and included in the NMA were provided by the company during clarification.
3.3 Were all relevant study results collected for use in the synthesis?	**Yes.** All included studies are reported in the synthesis and NMA.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Probably Yes**. CS states “A complete quality assessment in accordance with the NICE-recommended checklist for assessment of bias in RCTs is presented.” The ERG independently assessed using the NICE preferred checklist,

	Cochrane risk of bias tool which included additional signalling questions and overall ratings for each domain.[20]
3.5 Were efforts made to minimise error in risk of bias assessment?	**Yes.** Two independent reviewers conducted quality assessment for each included study at study level, with any disagreements discussed and resolved between them
Domain 3 risk of bias	**Unclear**
4: Synthesis and findings	
4.1 Did the synthesis include all studies that it should?	**Yes.** The search queries are suggestive of a very sensitive search which would mean a very low probability that potentially relevant studies were missed
4.2 Were all predefined analyses followed or departures explained?	**Yes.** In Appendix D, table 20, the planned analyses are outlined. There is no evidence to suggest that the planned analyses were not adhered to
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**Yes.** The synthesis was appropriate
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Yes**. Between-studies variation was addressed. Both fixed-effects and random-effects NMAs were performed. Random-effects was applied.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	**Yes.** Sensitivity analyses was performed
Domain 4 risk of bias	**Low**
Overall risk of bias in the review	**Low**

2.1.1 Searches

Searches in an appropriate set of bibliographic databases were undertaken between 8-10th May 2020. Bibliographic database searches are clearly reported and were conducted separately in each database. Suitable terms for the condition, treatments and study types (RCTs or systematic reviews or meta-analyses) were combined appropriately. Terms for most NICE comparators, plus an additional treatment, were included and match those listed as interventions in the company SR inclusion criteria (Table 6, CS Appendix D). Terms for statins were not included, although they are listed as a comparator in the CS scope (SoC, comprising of maximally tolerated statins with or without ezetimibe). Searches of Medline, Embase and Cochrane were not limited by date or language, although Embase searches included a limit to remove conference abstracts. The CS reports the search methods and totals retrieved for additional searches of 6 relevant conferences, the Conference Proceedings Citation Index- Science and two trials registers. The CS then states briefly that

searches of reference lists of clinical practice guidelines, reviews and other relevant studies, and key HTA body websites were undertaken, but search terms and results are not all clearly reported for these. The overall number found from these additional searches is given in the top right box of the PRISMA diagram (CS Appendix D, figure 1), but it is not clear how many (if any) of the included studies were found via these sources.

2.1.2 Inclusion criteria

The eligibility criteria for study inclusion and exclusion were defined according to patient, intervention, comparators, outcomes, and study design (PICOS) framework (CS Appendix D, Table 6, page 11).

Briefly, the inclusion criteria were publications in adults (≥18 years) with atherosclerotic cardiovascular disease (ASCVD) or elevated risk patients with a history of heterozygous familial hypercholesterolemia (HeFH) who has uncontrolled LDL-C on maximally tolerated dose statins or who are statin-intolerant. The patients with homozygous familial hypercholesterolemia, with no prior statin treatment (unless intolerant/contraindicated) or low-intensity statins at the background, at LDL-C targets on existing therapy, or those bearing other complications including organ transplantations, infectious diseases eg. HIV/AIDS, NYHA grade III-IV heart failure and stage 4/ 5 renal dysfunction have been excluded. It is worth mentioning that even though the pre-2015 SLRs, SLRs with no relevant information and trials that are yet to report data or not reported separately (ineligible as pool-analysis) were not eligible to be included in the CS SLR, the guidelines, and SLR/ NMAs were identified and hand-searched for relevant data, before being excluded.

The intervention includes inclisiran, evolocumab (Repatha®), alirocumab (Praluent®), ezetimibe (Ezetrol®), bempedoic acid (Nexletol®/Nilemdo®), and icosapent ethyl (Vascepa®) single or in combination and the only restriction concerning this matter is the doses and/ or frequencies that are not licensed (current or pending) in the US and/ or EU. Any paper at full-text sorting reporting on an intervention not listed in the NICE scope was excluded unless they pertained to information relevant to this review. The company did not report what information from papers including ineligible interventions might have been relevant. The inclusion criteria did not limit by comparators which were mentioned as the listed interventions plus other lipid-modifying treatments (LMTs) and placebo. However, icosapent ethyl (Vascepa®) and bempedoic acid (Nexletol®/Nilemdo®) most relevant articles concerning their role as comparators due to further PICOS modifications (retrospective criteria that are justified by the NICE scope) were considered ineligible.

An eligible study had to report outcomes in the areas of:

- % Change from baseline (CFB) in LDL-C

- Absolute CFB in LDL-C
- Time adjusted LDL-C CFB
- Proportion of patients meeting LDL-C targets
- VLDL-C
- HDL-C
- non-HDL-C
- Apolipoprotein-B and -A1 (ApoB, Apo-A1)
- Lipoprotein (a) [Lp(a)]
- Total cholesterol
- Triglycerides
- PCSK9
- High sensitivity C-reactive protein (hsCRP)
- CV events
- AEs, TRAEs, SAEs
- Discontinuation due to AE
- CV-related and non-CV-related mortality
- HRQoL

In terms of study design, the company included RCTs and excluded non-RCTs, less than 12 weeks of follow-up, and less than 10 patients per group. **The ERG believes that the exclusion of non-randomized studies is justified owing to the risk of these studies presenting inadequate control of biases that could threaten the validity of treatment comparisons.**

Full details of the study eligibility criteria are provided in CS Appendix D (Table 6, page 11).

The final inclusion criteria used by the company in their literature review largely reflects the NICE scope, but subcategorised the population into ASCVD and HeFH groups and removed aphersis as an outcome. Furthermore, a date limit of 2015 was applied to all SLRs. **The ERG considers the inclusion criteria to be appropriate with a low risk of biases and further explanations concerning the ineligible studies.**

The study selection process was performed at abstract and full-text levels. Initially, two independent reviewers screened all the studies identified in the searches of bibliographic records at the abstract level. Full texts of all potentially eligible abstracts which passed to the second stage of screening were reviewed by two independent reviewers using the pre-specified eligibility criteria. Disagreements regarding inclusion/exclusion of any given abstract or a full-text record at both levels of screening were discussed and reconciled between the two reviewers or with a help of a third reviewer. The company provided a

graphical display of the study selection process using a PRISMA study flow diagram (CS Appendix D, page 16). The list of excluded studies (at full-text review) with reasons for exclusions were provided (CS Appendix D, Table 13, page 38).

2.1.3 Critique of data extraction

The CS reports initial data extraction by two independent reviewers, which was later changed to full extraction by one reviewer with second reviewer checking due to time restraints (section D1.4, p14 CS appendix D). While full independent extraction is more systematic, data checking is still an acceptable method of extraction.

2.1.4 Quality assessment

The company's assessment of study quality of the included studies (section D.1.8, p109 CS appendix D) are summarised in Table 4 together with the ERG's independent assessment (appendix 1 ERG report). The company state they used the criteria set out in the NICE user guide for company evidence submission. They have assessed the RoB in the three included trials for Inclisiran (ORION 9,10,11) identified by the SLR.[19] [17] The latest NICE guidance recommends the Cochrane RoB tool as the preferred checklist, although the domains from the checklist were missed and the tool was not used in the manner in which it was designed.[20] However, the ERG included and assessed the missed domains. Two independent reviewers conducted quality assessment for each included study at study level, with any disagreements discussed and resolved between them. Reasons for ratings for each study have been provided by the company in Appendix D (page 166-168). Two ERG reviewers independently assessed the Risk of Bias (RoB) of the Orion 9, 10 and 11 trials using the RoB tool as recommended by NICE (detailed ERG assessment is available in Appendix 1).[20]

The ORION trials were assessed across the domains of randomization, allocation concealment, blinding (participants, study personnel, and outcome assessors), the similarity of groups at baseline, sample attrition/incomplete outcome data (Intention To Treat [ITT] analysis, sensitivity analysis), and selective outcome reporting (CS Appendix D page 166 Table 39). The company state that two researchers independently conducted quality assessment for each included study, at study level (CS Appendix D1.8).

Even though the CS assessed all domains of the ORION trials to be at low RoB, the ERG downgraded the quality of evidence in comparison to the company as some ambiguous

concepts or potential risks of biases. The prognostic factors and pathogenic mutations were not similar between groups and as a result, the ERG considers the ORION-9 at high risk of selection bias. Moreover, the performance bias is at high risk for the ORIONs due to the concomitant permitted medications which might cause the LDL-C false report. It is unclear whether there is potential attrition or detection bias for the three trials due to lack of the proper information concerning withdrawn participants and no evidence to support the investigator's blindness to prognostic factors.

The ERG partially agrees with some of the RoB sub-domains (appendix 1) assessed by the company. **Overall, the ERG has no concerns with the quality of these studies**.

Table 4. ERG summary assessment of ORION-9,10 and 11 trials quality (detailed assessment in appendix 1)

	ORION-9		ORION-10		ORION-11	
NICE Checklist item overall rating	CS judgement and rationale	ERG judgement and rationale	CS judgement and rationale	ERG judgement and rationale	CS judgement and rationale	ERG judgement and rationale
Selection bias (*randomization, concealment, group similarity*)	NR	Some concerns Based on the evidence that was provided by the company, classifying participants as HeFH without a pathogenic mutation or testing is considered high at risk of selection. Furthermore, no appropriate adjustments have been taken for ASCVD participants between the placebo and treatment.	NR	Low risk of bias	NR	Low risk of bias
Performance bias (*same care across groups, blinding of participants, blinding of treatment delivery*)	NR	Unclear Even though the company has gone through minimizing the performance bias, the ERG did not find sufficient evidence to support that groups were balanced. Moreover, concomitant permitted medications effect on study outcomes were found unclear.	NR	Unclear Even though the company has gone through minimizing the performance bias, the ERG did not find sufficient evidence to support that groups were balanced. Moreover, concomitant permitted medications effect on study outcomes were found unclear.	NR	Unclear Even though the company has gone through minimizing the performance bias, the ERG did not find sufficient evidence to support that groups were balanced. Moreover, concomitant permitted medications effect on study outcomes were found unclear

Attrition bias (*length of follow-up, groups comparability*)	NR	Unclear Even though the discontinuation rate between groups was not found significantly different, the ERG could not collate further information concerning participants' characteristics who were withdrawn from the study.	NR	Unclear Even though the completion rates were almost the same for both groups, the characteristics of withdrawn participants were ambiguous and the ERG could not collate any information about them.	NR	Unclear Even though the completion rates were almost the same for both groups, the characteristics of withdrawn participants were ambiguous and the ERG could not collate any information about them.
Detection bias (*length of follow-up, outcome definition, outcome methodology, blinding of investigators)*	NR	Unclear The company has provided proper considerations to reduce detection bias. Nonetheless, the ERG found no evidence to support the investigator's blindness to prognostic factors.	NR	Unclear The company has provided proper considerations to reduce detection bias. Nonetheless, the ERG found no evidence to support the investigator's blindness to prognostic factors.	NR	The company has provided proper considerations to reduce detection bias. Nonetheless, the ERG found no evidence to support the investigator's blindness to prognostic factors.
Questions listed on the company submission, not from the preferred NICE checklist						
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes- low RoB "All pre-specified outcomes reported"	Yes The ERG found listed primary, secondary, and exploratory objectives and outcomes completely reported without missing.[19]	Yes- low RoB "All pre-specified outcomes reported"	Yes The ERG found listed primary, secondary, and exploratory objectives and outcomes completely reported without missing.[17]	Yes- low RoB "All pre-specified outcomes reported"	Yes The ERG found listed primary, secondary, and exploratory objectives and outcomes completely reported without missing. [17]

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes- low RoB "All subjects randomized into the study comprised the intent-to-treat (ITT) population. Multiple imputation washout model was used to impute missing values for primary outcomes, control-based pattern mixture model was used to impute missing values for secondary outcomes"	Yes Raal et al have used multiple imputation washout models for missing data. They have considered the intention-to-treat population for the primary efficacy analysis.[19] "The washout model was performed on actual values; change and percentage change values were calculated after the imputation" for missing data analysis. "In addition, sensitivity analyses using mixed-effect models for repeated measures (MMRM) without multiple imputations and a control-based pattern mixture model (PMM) was performed on the co-primary and key secondary efficacy endpoints to assess the impact of missing values."	Yes- low RoB "An ITT population is used. All subjects randomized into the study comprised the ITT Population. The first primary efficacy end point was analysed with the use of an analysis-of-covariance model, and the second primary efficacy end point was analysed with the use of a mixed model for repeated measures, both with multiple imputation of data"	Yes Ray et al have used multiple imputation washout models for missing data. They have considered the intention-to-treat population for the primary efficacy analysis. Mixed-effect models for repeated measures (MMRM) have been used on the percent change in LDL-C from baseline to Day 510 to test the superiority of inclisiran over placebo after missing data imputation. Missing data were imputed using multiple imputation washout models. Results were combined using Rubin's method. [17]	Yes- low RoB "An ITT population is used. All subjects randomized into the study comprised the ITT Population. The first primary efficacy end point was analysed with the use of an analysis-of-covariance model, and the second primary efficacy end point was analysed with the use of a mixed model for repeated measures, both with multiple imputation of data."	Yes Ray et al have used multiple imputation washout models for missing data. They have considered the intention-to-treat population for the primary efficacy assessment by considering the analysis-of-covariance model. Mixed-effect models for repeated measures (MMRM) have been used on the percent change in LDL-C from baseline to Day 510 to test the superiority of inclisiran over placebo after missing data imputation. Missing data were imputed using multiple imputation washout models. Results were combined using Rubin's method.[17]

2.1.5 Evidence synthesis

2.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

Evidence for the clinical effectiveness of inclisiran comes from three RCTs: ORION-9, ORION-10 and ORION-11, Table 5 describes the overall methodological summary of the three studies.

Study objectives

In ORION-9, the use of inclisiran was evaluated "in a large cohort of adult patients with heterozygous familial hypercholesterolemia who had been treated with a maximally accepted dose of statin therapy."

"The objectives of the ORION-10 and ORION-11 trials were to assess the efficacy, safety, and adverse-event profile of inclisiran over a period of 18 months in patients at high risk for cardiovascular disease in whom LDL cholesterol levels were elevated despite receiving statin therapy at the maximum tolerated dose with or without additional lipid-lowering therapy."

Table 5. ORION-9,10,11 design summary

	ORION 9 (NCT03397121)	**ORION 10 (NCT03399370)**	**ORION 11 (NCT03400800)**
Study design	Randomised, double blind, placebo-controlled, Phase 3 trial		
Intervention	Inclisiran 284 mg (delivered via a single subcutaneous injection every 6 months after an initial dose (day 1) and another dose after 3 months)		
Comparator	Placebo (0.9% sodium chloride in water solution administered in the 1.5 ml volume)		
Start and completion dates	[redacted]	[redacted]	[redacted]
Sample size	482 participants (n=242 inclisiran vs n=240 placebo)	1561 participants (n=781 inclisiran vs n=780 placebo)	1617 participants (n=810 inclisiran vs n=807 placebo)
Study duration	18 months (540 days)	18 months (540 days)	18 months (540 days)
Population	Adults with HeFH and elevated LDL-C	Adults with ASCVD and elevated LDL-C	Adults with ASCVD or ASCVD-RE (termed PPER within this submission) and elevated LDL-C
Countries (number of centers)	8 countries across Europe, South Africa and North America (47 centers) (UK sites: 0)	United States of America only (146 centers) (UK sites: 0)	8 countries across Europe, South Africa and North America (72 centers) (UK sites: 23-462 patients)
Inclusion criteria	Subjects with history of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented	Subjects with history of ASCVD, and serum LDL ≥1.8 mmol/l.	Subjects with history of ASCVD or ASCVD-RE (T2D, FH, and including patients whose 10-year

	history of untreated LDL-C of >4.9 mmol/l (190 mg/dl), and a family history of FH, elevated cholesterol, or early heart disease, and serum LDL ≥2.6 mmol/l. Other inclusion criteria were patients on statins should have been receiving a maximally tolerated dose, and patients not receiving statins must have had documented evidence of intolerance to all doses of at least two different statins.	Other inclusion criteria were patients on statins should have been receiving a maximally tolerated dose, and patients not receiving statins must have had documented evidence of intolerance to all doses of at least two different statins.	risk of a CV event assessed by Framingham Risk Score or equivalent has a target LDL-C of <2.6 mmol/l, and serum LDL ≥1.8 mmol/l for ASCVD patients or ≥2.6 mmol/l for ASCVD risk-equivalent patients at screening. Other inclusion criteria were patients on statins should have been receiving a maximally tolerated dose, and patients not receiving statins must have had documented evidence of intolerance to all doses of at least two different statins.
Key primary endpoints	1) % Change from baseline (CFB) in LDL-C to Day 510 2) Time adjusted LDL-C CFB after Day 90 and up to Day 540		
Key secondary endpoints	1) Absolute CFB in LDL-C to Day 510 2) Time adjusted absolute CFB in LDL-C after Day 90 and up to Day 540 3) CFB in PCSK9, total cholesterol, Apo-B, and non-HDL-C to Day 510		
Exclusion criteria	1) Subjects having a known underlying disease that may interfere with the clinical study results, 2) Treatment within monoclonal antibodies directed towards PCSK9 within the last 90 days prior to screening, 3) Treatment with other investigational products within 30 days or five half-lives of screening visit or planned use of other investigational products during the course of the ORION studies.		
Randomization	Subjects were randomized by an automated Interactive Response Technology (IRT)		
Blinding	Double-blind study that subjects, the clinical study site pharmacist and care providers have been blinded. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions.		

Study design and treatment

ORION-9, ORION-10 and ORION-11 (NCT03397121, NCT03399370, and NCT03400800 respectively) were phase III, randomised, double-blind, placebo-controlled trials.

Inclisiran is licensed for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

Inclisiran is delivered via a single subcutaneous injection with the recommended dose of 284 mg (equivalent to 300 mg/1.5 ml of Inclisiran) administered every 6 months after an initial dose (day 1) and another dose after 3 months. The comparator in the three ORION trials was placebo which was a 0.9% sodium chloride in water solution administered in the same

1.5 ml volume and packaged in the same container as inclisiran to maintain blinding. The dosing regimen is presented in figure 5 of the CS (Section B.2.3.1; page 53).

According to the cover pages of their respective CSRs, the starts of the studies (date when the first subject was randomised) and completion dates (date of the last subject, last visit) were:

[redacted]

[redacted]**Randomisation**

All three ORION trials (ORION-9, ORION-10 and ORION-11) randomized patients via an automated Interactive Response Technology (IRT). Patients were assigned in a 1:1 ratio to either inclisiran sodium (300mg) or matching placebo. All the trials stratified treatment allocation by current use of statins or other lipid-modifying therapies in block sizes of 4. Additionally, the ORION-9 and ORION-11 trials stratified treatment allocation by country.

Blinding

All three ORION trials were double-blind placebo-controlled studies. Patient were blind to their treatment allocation following randomised assigning. Clinical study site pharmacists maintained the double blind using pre-specified site-specific procedures. Treatments were blinded prior to arrival on site via the use of a yellow shroud. Additionally, blinded syringes were provided to maintain blinding. Only the principal investigator was authorised via the IRT to unblind a subject in the event of an emergency or adverse event. There was no mention in any of the trials that the investigators were blind to important confounding and prognostic factors such as concomitant lipid-modifying therapy or number of cardiovascular risk factors.

Selection of participants

Key inclusion and exclusion criteria for ORION-9, -10, and-11 are presented in CS Table 9 (section B.2.3.3; page 56). Most of the criteria are identical except for disease history and serum LDL levels to reflect the indications in each trial as specified in Table 5.

Other inclusion criteria were patients on statins should have been receiving a maximally tolerated dose, and patients not receiving statins must have had documented evidence of intolerance to all doses of at least two different statins.

Patient disposition for the three key trials in this submission are presented in section B.2.6 of the CS (page 67) and figure 6 (section B.2.6.1.1; page 68), 10 (section B.2.6.2.1; page 78) and 14 (section B.2.6.3.1; page 89) of the CS. In ORION-9, a total of 482 participants were randomised to either inclisiran (n=242; 50.2%) or placebo (n=240; 49.8%). In ORION-10, a total of 1561 participants were randomised to either inclisiran (n=781; 50.0%) or placebo

(n=780; 50.0%). In ORION-11, a total of 1617 participants were randomised to either inclisiran (n=810; 50.1%) or placebo (n=807; 49.9%).

Locations

ORION-9 and ORION-11 were international and multi-centred, both having been undertaken in 8 countries across Europe, South Africa and North America. ORION-10 recruited study participants in the United States of America only.

Data in the CS are presented as of the end of study dates as listed above.

The baseline characteristics of patients in all three ORION trials, split by treatment group, are presented in Table 12 of the CS (section B.2.6.3; page 59). **Overall, the baseline characteristics within trials were comparable.**

2.2.1 Non RCTs

The CS does not include any non-RCTs that provide evidence for inclisiran (described earlier in 2.1.2).

2.2.2 Ongoing studies

As stated in section B.2.11 (page 151) of the CS, the following studies are ongoing and future which are relevant to the decision problem:

- ORION-4: a double-blind, randomised placebo-controlled assessment of the effects of inclisiran on clinical outcomes in approximately 15,000 patients with pre-existing ASCVD, status: ongoing; anticipated end date: December 2024.
- ORION-8: an open-label extension study for patients who completed ORION-9, -10 and –11, to evaluate the efficacy, safety and tolerability of long-term dosing of inclisiran, ongoing; anticipated end date: December 2023.
- SPIRIT: a future study which will focus on testing intervention with inclisiran in primary care. The ERG could not locate the trial registry.

The ERG also undertook a targeted search for inclisiran terms only (Medline, Embase and Google.com, search date 19th Nov 2020 with auto-alerts from each checked up to 11th Jan 2020). The ERG found 3 relevant meta-analyses undertaken since the company search, however there were no new studies suitable for inclusion within them.[21-23] The ERG also found a published abstract of an NMA, not relevant for inclusion, but believes there may be a related full paper which would require reference checking out in the near future.[24]

2.2.3 Description and critique of the company's outcome selection

The NICE scope outcomes can be found in section 1.4.4 and Table 2.

Outcomes in the company submission are the same as listed in the NICE scope with the exception of LDL apheresis, the ERG agree that this was appropriate (full details can be found in section 1.4.4).

Definitions of the outcomes included in this submission are as follows:

The co-primary outcomes were the percentage change in LDL-C from baseline to Day 510 and the time-adjusted percentage change in LDL-C from baseline after Day 90 and to Day 540.

Key secondary endpoints across all the ORION trials 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 and the percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B and non-HDL-C. Other secondary endpoints across all the ORION trials are listed in CS section B.2.3.2.3 (page 54).

Study-specific endpoints were:

- ORION-9: major adverse cardiac event, proportion of patients in each group with any LDL-C reduction from baseline at any visit, and response of LDL-C reduction by underlying causal mutations of HeFH,
- ORION-10: MACE,
- ORION-11: MACE, and the proportion of patients in each group with any LDL-C reduction from baseline at any visit.

Health-related quality of life data was not available from ORION in the CS; therefore, the company conducted an SLR to identify HRQoL studies relevant to the decision problem, detail of which is presented in the company's appendix H,

Safety of inclisiran was assessed by observing the frequency of TEAEs and SAEs between the two treatment groups and provided in further detail in section B.2.10 (page 143) of the CS.

Overall, the outcomes selected in the CS were consistent with that of the NICE scope.

2.2.4 Summary and critique of the company's approach to statistical analysis and results

2.2.4.1 Company submission

The company provided data to the ERG in the following 2 submissions:

- ID1647 inclisiran Document B; version 1.0; 30/10/20
- ID1647 Responses to clarification questions; version 1.0; 03/12/20
- ID1647 Responses to clarification questions; version 1.0; 15/12/220.

2.2.4.2 Summary of trial statistics

The company's approach to trial statistics is presented in section B.2.4 (page 61) of the CS. The hypotheses that were tested for the two primary endpoints, and how they were analysed, were as follows:

- Null H_{01}: Difference between patient treated with inclisiran and placebo in the least squares mean percentage change in LDL-C from baseline at Day 510 equals zero
    - Alternative H_{A1}: Difference is less than zero

The analysis for the above outcome on the ITT population was based on an analysis of covariance (ANCOVA) model on each multiply imputed dataset (100 in total). The ANCOVA model included treatment group, current use of statins or other lowering therapy at baseline, and baseline LDL-C levels as covariates.

Null H_{02}: Difference between patient treated with inclisiran and placebo in the least squares mean time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 equals zero

- Alternative H_{A2}: Difference is less than zero

The analysis for the second primary outcome was also conducted on the ITT population and based on mixed-effect models for repeated measures over all visits on each multiply imputed dataset (100 in total). The model included treatment, visit, baseline value of LDL-C, current use of statins or other lipid lowering therapy, and an interaction between treatment and visit as covariates.

Details of the analysis of the secondary endpoints are presented in section B.2.4.6 (page 65) of the CS and were only to be tested if there was evidence to reject any (or both) of the null hypotheses for the co-primary endpoints.

The absolute change in LDL-C form baseline to Day 510 and percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B, and non-HDL-C was analysed using

an MMRM with the following covariate: treatment, visit, baseline value, and treatment-by-visit interaction (as clarified in question A15 of clarification responses). The time-adjusted absolute change in LDL-C was analysed using a similar method to the second co-primary endpoint. Odds ratios and 95% CIs were calculated for binary variables using logistic regression models.

The subgroups considered as part of the company's decision problem are presented in Table 1 (section B.1.1; page 17) of the CS.

Missing data for the co-primary and key secondary outcomes were imputed.

Sample size calculations: it was calculated that approximately 380 patients would be needed for ORION-9 and 1,425 patients for ORION-10 and ORION-11.

The ERG believes the company's approach to trial statistics for the key ORION trials are appropriate. Methods for analysing the outcomes, imputation, sample size calculations, and quality assessment were all appropriate.

2.2.5 Summary of trial results

A summary of key outcomes are presented in Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, and Table 12.

2.2.5.1 Co-primary endpoints

Treatment with inclisiran resulted in statistically significant decreases in LDL-C levels (change in LDL-C and the time-adjusted percentage change) across all three ORION trials for both co-primary endpoints. The results of the analyses of the co-primary endpoints for all three ORION trials (-9, -10 and -11) are presented in Table 6 of the ERG report.

2.2.5.1.1 ORION-9

The percentage change in LDL-C from baseline to Day 510 in the inclisiran group was a 39.7% decrease compared to an increase of 8.2% in the placebo group, resulting in a statistically significant between group difference of -47.9% (95% CI: -53.5 to -42.3%; p<0.001).

The time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 in the inclisiran group was a 38.1% decrease compared to an increase of 6.2% in the placebo group, resulting in a statistically significant between group difference of -44.3% (95% CI: -48.5 to -40.1%; p<0.001).

2.2.5.1.2 ORION-10

The percentage change in LDL-C from baseline to Day 510 in the inclisiran group was a 51.3% decrease compared to an increase of 1.0% in the placebo group, resulting in a statistically significant between group difference of -52.3% (95% CI: -55.7 to -48.8%; p<0.001).

The time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 in the inclisiran group was a 51.3% decrease compared to an increase of 2.5% in the placebo group, resulting in a statistically significant between group difference of -53.8% (95% CI: -56.2 to -51.3%; p<0.001).

2.2.5.1.3 ORION-11

The percentage change in LDL-C from baseline to Day 510 in the inclisiran group was a 45.8% decrease compared to an increase of 4.0% in the placebo group, resulting in a statistically significant between group difference of -49.9% (95% CI: -53.1 to -46.6%; p<0.001).

The time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 in the inclisiran group was a 45.8% decrease compared to an increase of 3.4% in the placebo group, resulting in a statistically significant between group difference of -49.2% (95% CI: -51.6 to -46.8%; p<0.001).

2.2.5.1.4 Sensitivity analyses

Pre-specified sensitivity analyses were performed for each of the co-primary outcomes which assessed how the results differed when using three different methods to handle for missing data. Results of which are presented in Table 7. For all the endpoints in all three ORION trials, the results, specifically the inclisiran minus placebo differences, were like that in the primary analyses.

Table 6: A summary of the co-primary endpoints of the pivotal ORION trials

	ORION-9			ORION-10			ORION-11		
	Inclisiran (N=242)	**Placebo (N=240)**	**Difference***	**Inclisiran (N=781)**	**Placebo (N=780)**	**Difference***	**Inclisiran (N=810)**	**Placebo (N=807)**	**Difference***
Percentage change in LDL-C from baseline to Day 510									
Percentage change (95% CI)	-39.7 (-43.7, -35.7)	8.2 (4.3, 12.2)	-47.9 (-53.5, -42.3)	-51.3 (-53.8, -48.8)	1.0 (-1.5, 3.4)	-52.3 (-55.7, -48.8)	-45.8 (-48.2, -43.5)	4.0 (1.8, 6.3)	-49.9 (-53.1, -46.6)
P-value			<0.001			<0.001			<0.001
Time-adjusted percentage change in LDL-C from baseline after day 90 and up to Day 540									
Percentage change (95% CI)	-38.1 (-41.1, -35.1)	6.2 (3.3, 9.2)	-44.3 (-48.5, -40.1)	-51.3 (-53.0, -49.5)	2.5 (0.8, 4.3)	-53.8 (-56.2, -51.3)	-45.8 (-47.5, -44.1)	3.4 (1.7, 5.1)	-49.2 (-51.6, -46.8)
P-value			<0.001			<0.001			<0.001

*Difference = inclisiran – placebo

Table 7: Sensitivity analyses results of the co-primary endpoints of the ORION trials

	ORION-9			ORION-10			ORION-11		
	Inclisiran (N=242)	**Placebo (N=240)**	**Difference***	**Inclisiran (N=781)**	**Placebo (N=780)**	**Difference***	**Inclisiran (N=810)**	**Placebo (N=807)**	**Difference***
Percentage change in LDL-C from baseline to Day 510									
Sensitivity 1: Control-based PMM									
LSM (95% CI)	–39.7 (–43.7, –35.7)	8.27 (4.32, 12.23)	–48.0 (–53.6, –42.4)	–53.5 (–55.8, –51.1)	1.0 (–1.3, 3.4)	–54.5 (–57.8, –51.2)	–47.7 (–49.9, –45.5)	4.1 (1.9, 6.3)	–51.8 (–54.9, –48.7)
P-value			< 0.0001			<0.0001			<0.0001
Sensitivity 2: MMRM									
LSM (95% CI)	–40.8 (–44.6, –36.9)	8.06 (4.16, 11.96)	–48.8 (–54.3, –43.3)	–56.2 (–58.4, –54.0)	1.1 (–1.2,3.3)	–57.2 (–60.4, –54.1)	–48.8 (–51.0, –46.6)	3.9 (1.7, 6.0)	–52.7 (–55.7, –49.6)
P-value			< 0.0001			<0.0001			<0.0001

Sensitivity 3: ANCOVA from multiple imputation washout model including country									
LSM (95% CI)	–39.5 (–44.7, –34.2)	8.44 (2.99, 13.88)	–47.9 (–55.5, –40.3)	–45.5 (–49.3, –41.7)	6.8 (3.0, 10.6)	–52.3 (–55.7, –48.9)	–48.0 (–51.9, –44.0)	1.9 (–1.8, 5.7)	–49.9 (–55.3, –44.5)
P-value			< 0.0001			<0.0001			<0.0001
Time-adjusted percentage change in LDL-C from baseline to Day 510									
Sensitivity 1: MMRM									
LSM (95% CI)	–38.5 (–41.4, –35.6)	6.3 (3.34, 9.2)	–44.8 (–48.9, –40.6)	–53.2 (–54.8, –51.5)	2.7 (1.1, 4.4)	–55.9 (–58.2, –53.5)	–46.6 (–48.3, –44.9)	3.4 (1.7, 5.0)	–49.9 (–52.3, –47.6)
P-value			< 0.0001			<0.0001			<0.0001
Sensitivity 2: Control-based PMM including country									
LSM (95% CI)	–36.8 (–40.5, –33.1)	5.1 (1.1, 9.0)	–41.9 (–47.3, –36.4)	–46.3 (–48.9, –43.8)	7.5 (4.9, 10.1)	–53.8 (–56.2, –51.4)	–47.4 (–50.2, –44.5)	4.1 (1.3, 6.8)	–51.4 (–55.4, –47.4)
P-value			< 0.0001			<0.0001			<0.0001
Sensitivity 3: Two sample t-test									
LSM (95% CI)	–38.0 (–40.6, –35.4)	6.1 (2.9, 9.4)	–44.2 –48.3, –40.0)	–51.3 (–52.9, –49.6)	2.5 (0.6, 4.4)	–53.8 (–56.2, –51.3)	–46.0 (–47.5, –44.5)	3.5 (1.6, 5.4)	–49.5 (–51.9, –47.1)
P-value			< 0.0001			<0.0001			<0.0001

*Difference = inclisiran – placebo

2.2.5.2 Key secondary endpoints

Treatment with inclisiran resulted in statistically significant decreases in LDL-C, PCSK9, total cholesterol, apolipoprotein-B and non-HDL-C levels from baseline across all three ORION trials compared to placebo ($p<0.0001$ for all outcomes across all of the outcomes in favour of inclisiran). The results of the analyses of the key-secondary endpoints for all three ORION trials (9-, -10 and -11) are presented in Table 8 of the ERG report.

Table 8: Results of the analyses of the key secondary endpoints for the ORION trials

	ORION-9			ORION-10			ORION-11		
	Inclisiran (N=242)	**Placebo (N=240)**	**Difference**	**Inclisiran (N=781)**	**Placebo (N=780)**	**Difference**	**Inclisiran (N=810)**	**Placebo (N=807)**	**Difference**
Absolute change in LDL-C from baseline to Day 510 using a control-based PMM									
Change (95% CI)	-1.5	0.3	-1.8 (-2.0, -1.6)	-1.5	-0.1	-1.4 (-1.5, -1.3)	-1.3	0.03	-1.3 (-1.4, -1.3)
P-value			<0.001			<0.001			<0.001
Time-adjusted absolute change in LDL-C from baseline after day 90 and up to Day 540 using a control-based PMM									
Change (95% CI)	-1.5	0.1	-1.6 (-1.8, -1.5)	-1.4	-0.01	-1.4 (-1.4, -1.3)	-1.3	0.01	-1.3 (-1.3, -1.2)
P-value			<0.001			<0.001			<0.001
Percentage change from baseline to Day 510 in PCSK9									
LSM (95% CI)	–60.7 (–64.4, –57.0)	17.7 (13.9, 21.4)	–78.3 (–83.7, –73.0)	–69.8 (–73.9, –65.7)	13.5 (9.3,17.8)	–83.3 (–89.3, –77.3)	–63.6 (–65.6, –61.7)	15.6 (13.7, 17.5)	–79.3 (–82.0, –76.6)
P-value			<0.0001			<0.0001			<0.0001
Percentage change from baseline to Day 510 in total cholesterol									
LSM (95% CI)	–25.1 (–27.8, –22.4)	6.7 (4.0, 9.4)	–31.8 (–35.6, –27.9)	–33.6 (–35.1, –32.0)	–0.4 (–2.0,1.1)	–33.1 (–35.3, –31.0)	–28.0 (–29.4, –26.6)	1.8 (0.4, 3.2)	–29.8 (–31.8, –27.8)
P-value			<0.0001			<0.0001			<0.0001
Percentage change from baseline to Day 510 in Apolipoprotein B									
LSM (95% CI)	–33.1 (–35.9, –30.4)	2.9 (0.1, 5.7)	–36.1 (–40.0, –32.1)	–44.8 (–46.5, –43.1)	–1.7 (–3.5,0.02)	–43.1 (–45.5, –40.7)	–38.2 (–39.8, –36.5)	0.8 (–0.8, 2.4)	–38.9 (–41.2, –36.7)
P-value			<0.0001			<0.0001			<0.0001
Percentage change from baseline to Day 510 in Non-HDL-C									
LSM (95%	–34.9 (–38.5, –	7.4 (3.9, 10.9)	–42.4 (–47.3, –	–47.4 (–49.4, –	–0.1 (–2.1,2.0)	–47.4 (–50.3, –	–41.2 (–43.1, –	2.2 (0.2, 4.1)	–43.3 (–46.0, –

CI)	31.4)		37.4)	45.4)		44.5)	39.2)		40.6)
P-value			<0.0001			<0.0001			<0.0001

2.2.5.3 Other secondary endpoints

Treatment with inclisiran resulted in statistically significant decreases in the other secondary endpoints across all three ORION trials compared to placebo. The results of the analyses of the key-secondary endpoints for all three ORION trials (9-, -10 and -11) are presented in Table 9, Table 10, of the ERG report.

2.2.5.3.1 ORION-9

Results of the other secondary endpoints for ORION-9 are presented in Table 9.

Figure 9 of the CS (section B.2.6.1.4.1; page 74) presents a waterfall plot of absolute change in LDL-C from baseline to Day 510 for all subjects in ORION-9. A much larger proportion of the inclisiran group had reduced levels of LDL compared to the placebo group, resulting in a placebo-adjusted percentage reduction in LDL-C from baseline of 39.1% to 50.5% ($p<0.001$ for all time points up to Day 540).

Placebo-adjusted absolute changes in PCSK9, total cholesterol, apolipoprotein B, lipoprotein-A (including percentage change) and non-HDL-C were all statistically significant.

A higher proportion of patients treated with inclisiran reached lower levels of LDL-C compared to placebo-treated patients (<100 mg/dl: 65.3% vs 8.8%). Moreover, a high proportion of inclisiran-treated patients (66%) had a 50% of higher reduction in LDL-C compared to the placebo group (4%), and a higher proportion of inclisiran-treated patients attained global lipid targets for their level of ASCVD risk compared to placebo-treated patients.

Table 9: Results of the analyses of other secondary endpoints for ORION-9

	ORION-9		
	Inclisiran	**Placebo**	**Difference**
Absolute change from baseline to Day 510 in PCSK9			
LSM (95% CI)	-282.6 (-297.9, -267.2)	54.5 (39.1, 70.0)	-337.1 (-358.9, 315.3)
P-value			<0.0001
Absolute change from baseline to Day 510 in total cholesterol			
LSM (95% CI)	-60.8 (-67.0, -54.7)	12.6 (6.4, 18.8)	-73.5 (-82.2, -64.7)
P-value			<0.0001
Absolute change from baseline to Day 510 in apolipoprotein B			
LSM (95% CI)	-42.5 (-46.0, -39.0)	1.9 (-1.6, 5.4)	-44.3 (-49.3, -39.4)
P-value			<0.0001
Absolute change from baseline to Day 510 in non-HDL-C			
LSM (95% CI)	-64.3 (-70.5, -58.2)	10.3 (4.1, 16.5)	-74.6 (-83.3, -65.9)
P-value			<0.0001
Individual responsiveness at Day 510, N (%)			

<25 mg/dl	2 (0.8)	0 (0.0)	
<50 mg/dl	46 (19.0)	2 (0.8)	
<70 mg/dl	99 (40.9)	3 (1.3)	
<100 mg/dl	158 (65.3)	21 (8.8)	
≥100 mg/dl	73 (30.2)	208 (86.7)	
Missing	11 (4.5)	11 (4.6)	
Proportion of patients in each group with greater or equal to 50% reduction in LDL-C reduction from baseline, N (%)			
Reduction from baseline at any visit	159 (66.0)	9 (3.8)	
Reduction from baseline at:			
Visit 3 Day 90	81 (33.8)	6 (2.5)	
Visit 4 Day 150	116/239 (48.5)	4/238 (1.7)	
Visit 5 Day 270	50/240 (20.8)	5/235 (2.1)	
Visit 6 Day 330	101/237 (42.6)	4/233 (1.7)	
Visit 7 Day 450	48/237 (20.3)	1/233 (0.4)	
Visit 8 Day 510	92/231 (39.8)	2/229 (0.9)	
Visit 9 Day 540	85/232 (36.6)	4/232 (1.7)	
Proportion of patients in each group who attain global lipid targets for their level of ASCVD risk, N (%)			
At any visit	186 (77.2)	44 (18.4)	
Patients with ASCVD			
At Day 510	31 (52.5)	1 (1.4)	
Patients with ASCVD risk-equivalent			
At Day 510	115 (66.9)	14 (8.9)	
Absolute change in lipoprotein-a from baseline to Day 540 using MMRM			
LSM (95% CI)	-16.0 (-20.0, -12.0)	-0.1 (-4.1, 3.9)	-15.9 (-21.5, -10.3)
P-value			< 0.0001
Percentage change in lipoprotein-a from baseline to Day 540 using MMRM			
LSM (95% CI)	-11.9 (-15.7, -8.1)	7.6 (3.8, 11.4)	-19.5 (-24.9, -14.1)
P-value			< 0.0001

2.2.5.3.2 ORION-10

Results of the other secondary endpoints for ORION-10 are presented in Table 10 and Table 9.

Figure 13 of the CS (section B.2.6.2.4.1; page 84) presents a waterfall plot of absolute change in LDL-C from baseline to Day 510 for all subjects in ORION-10. A much larger proportion of the inclisiran group had reduced levels of LDL compared to the placebo group, resulting in a placebo-adjusted percentage reduction in LDL-C from baseline of 48.5% to 61.4% ($p<0.001$ for all time points).

Placebo-adjusted absolute changes in PCSK9, total cholesterol, apolipoprotein B, lipoprotein-A (including percentage change) and non-HDL-C were all statistically significant.

A higher proportion of patients treated with inclisiran reached lower levels of LDL-C compared to placebo-treated patients (<100 mg/dl: 83.4% vs 49.6%). Moreover, a high proportion of inclisiran-treated patients (91%) had a 50% of higher reduction in LDL-C compared to the placebo group (7%), and a higher proportion of inclisiran-treated patients attained global lipid targets for their level of ASCVD risk compared to placebo-treated patients.

Table 10: Results of the analyses of other secondary endpoints for ORION-10

	ORION-10		
	Inclisiran	**Placebo**	**Difference**
Absolute change from baseline to Day 510 in PCSK9			
LSM (95% CI)	–316.1 (–328.1, –304.0)	17.9 (5.6, 30.2)	–333.9 (–351.1, –316.7)
P-value			<0.0001
Absolute change from baseline to Day 510 in total cholesterol			
LSM (95% CI)	–64.8 (–67.4, –62.1)	–3.2 (–5.9, –0.5)	–61.6 (–65.4, –57.8)
P-value			<0.0001
Absolute change from baseline to Day 510 in apolipoprotein B			
LSM (95% CI)	–44.7 (–46.3, –43.2)	–3.1 (–4.7, –1.5)	–41.7 (–43.9, –39.4)
P-value			<0.0001
Absolute change from baseline to Day 510 in non-HDL-C			
LSM (95% CI)	–67.3 (–69.9, –64.7)	–3.1 (–5.8, –0.5)	–64.2 (–67.9, –60.5)
P-value			<0.0001
Individual responsiveness at Day 510, N (%)			
<25 mg/dl	160 (20.5)	4 (0.5)	
<50 mg/dl	483 (61.8)	19 (2.4)	
<70 mg/dl	581 (74.4)	119 (15.3)	
<100 mg/dl	651 (83.4)	387 (49.6)	
≥100 mg/dl	40 (5.1)	279 (35.8)	
Missing	90 (11.5)	114 (14.6)	
Proportion of patients in each group with greater or equal to 50% reduction in LDL-C reduction from baseline, N (%)			
Reduction from baseline at any visit	701 (91.4)	50 (6.5)	
Reduction from baseline at:			
Visit 3 Day 90	503/758 (66.4)	13/762 (1.7)	
Visit 4 Day 150	584/757 (77.1)	17/745 (2.3)	
Visit 5 Day 270	391/737 (53.1)	17/724 (2.3)	

Visit 6 Day 330	513/731 (70.2)	14/715 (2.0)	
Visit 7 Day 450	382/721 (53.0)	18/698 (2.6)	
Visit 8 Day 510	503/691 (72.8)	17/666 (2.6)	
Visit 9 Day 540	482/705 (68.4)	18/670 (2.7)	
Proportion of patients in each group who attain global lipid targets for their level of ASCVD risk, N (%)			
At any visit	722 (94.1)	277 (36.1)	
Patients with ASCVD			
At Day 510	581 (84.1)	119 (17.9)	
Absolute change in lipoprotein-a from baseline to Day 540 using MMRM			
LSM (95% CI)	-25.9 (-28.7, -23.2)	0.5 (-2.3, 3.3)	-26.4 (-30.3, -22.5)
P-value			<0.0001
Percentage change in lipoprotein-a from baseline to Day 540 using MMRM			
LSM (95% CI)	-15.5 (-19.2, -11.8)	16.4 (12.6, 20.2)	-31.9 (-37.2, -26.5)
P-value			<0.0001

2.2.5.3.3 ORION-11

Results of the other secondary endpoints for ORION-11 are presented in Table 9 and Table 11

Figure 17 of the CS (section B.2.6.3.4.1; page 95) presents a waterfall plot of absolute change in LDL-C from baseline to Day 510 for all subjects in ORION-11. A much larger proportion of the inclisiran group had reduced levels of LDL compared to the placebo group, resulting in a placebo-adjusted percentage reduction in LDL-C from baseline of 42.5% to 54.2% ($p<0.001$ for all time points).

Placebo-adjusted absolute changes in PCSK9, total cholesterol, apolipoprotein B, lipoprotein-A (including percentage change) and non-HDL-C were all statistically significant.

A higher proportion of patients treated with inclisiran reached lower levels of LDL-C compared to placebo-treated patients (<100 mg/dl: 81.6% vs 52.7%). Moreover, a high proportion of inclisiran-treated patients (82%) had a 50% of higher reduction in LDL-C compared to the placebo group (6%), and a higher proportion of inclisiran-treated patients attained global lipid targets for their level of ASCVD risk compared to placebo-treated patients.

Table 11: Results of the analyses of other secondary endpoints for ORION-11

	ORION-11		
	Inclisiran	**Placebo**	**Difference**
Absolute change from baseline to Day 510 in PCSK9			
LSM (95% CI)	–245.1 (–250.9, –239.2)	40.7 (34.9, 46.5)	–285.8 (–294.0, –277.6)
P-value			<0.0001

Absolute change from baseline to Day 510 in total cholesterol			
LSM (95% CI)	–54.9 (–57.5, –52.3)	0.31 (–2.25, 2.88)	–55.2 (–58.9, –51.6)
P-value			<0.0001
Absolute change from baseline to Day 510 in apolipoprotein B			
LSM (95% CI)	–38.9 (–40.4, –37.4)	–1.2 (–2.7, 0.3)	–37.7 (–39.8, –35.5)
P-value			<0.0001
Absolute change from baseline to Day 510 in non-HDL-C			
LSM (95% CI)	–58.8 (–61.3, –56.2)	–0.5 (–3.1, 2.0)	–58.3 (–61.8, –54.7)
P-value			<0.0001
Individual responsiveness at Day 510, N (%)			
<25 mg/dl	95 (11.7)	1 (0.1)	
<50 mg/dl	420 (51.9)	19 (2.4)	
<70 mg/dl	564 (69.6)	104 (12.9)	
<100 mg/dl	661 (81.6)	425 (52.7)	
≥100 mg/dl	63 (7.8)	314 (38.9)	
Missing	86 (10.6)	68 (8.4)	
Proportion of patients in each group with greater or equal to 50% reduction in LDL-C reduction from baseline, N (%)			
Reduction from baseline at any visit	658 (81.9)	47 (5.9)	
Reduction from baseline at:			
Visit 3 Day 90	413/790 (52.3)	10/797 (1.3)	
Visit 4 Day 150	491/796 (61.7)	13/785 (1.7)	
Visit 5 Day 270	338/778 (43.4)	12/774 (1.6)	
Visit 6 Day 330	471/773 (60.9)	18/773 (2.3)	
Visit 7 Day 450	301/768 (39.2)	21/764 (2.7)	
Visit 8 Day 510	418/724 (57.7)	17/739 (2.3)	
Visit 9 Day 540	420/742 (56.6)	19/749 (2.5)	
Proportion of patients in each group who attain global lipid targets for their level of ASCVD risk, N (%)			
At any visit	741 (92.4)	335 (41.9)	
Patients with ASCVD			
At Day 510	522 (81.7)	103 (16.0)	
Patients with ASCVD risk-equivalent			
At Day 510	66 (77.6)	29 (30.5)	
Absolute change in lipoprotein-a from baseline to Day 540 using MMRM			
LSM (95% CI)	-17.2 (-21.4, -12.9)	-2.4 (-6.7, 1.9)	-14.8 (-18.3, -11.2)
P-value			<0.0001
Percentage change in lipoprotein-a from baseline to Day 540 using MMRM			
LSM (95% CI)	-9.9 (-15.2, -4.6)	9.2 (3.8, 14.5)	-19.1 (-23.6, -14.6)
P-value			<0.0001

2.2.5.4 Other exploratory endpoints

Section B.2.3.2.4 (page 55) of the CS lists the exploratory endpoints for ORION-9, -10 and -11, and Table 12 presents the results of the exploratory analyses.

The proportions of major adverse cardiac events in ORION-9 were similar between groups but were higher in the inclisiran groups in ORION-10 and ORION-11 compared to the respective placebo groups.

In ORION-9, all but two patients responded to inclisiran by having a reduction in LDL-C levels at any time during the study. In ORION-11, all but five patients responded to inclisiran treatment.

Table 12: Results of exploratory analyses for the ORION trials

	ORION-9		ORION-10		ORION-11	
	Inclisiran	**Placebo**	**Inclisiran**	**Placebo**	**Inclisiran**	**Placebo**
MACE events, N (%)	10 (4.1)	10 (4.2)	79 (10.2)	58 (7.4)	83 (10.3)	63 (7.8)
Any reduction in LDL-C from baseline at any visit (responders), N (%)	239 (99.2)	NA	-	-	797 (99.4)	NA

2.2.5.5 Subgroup analyses

The subgroups reported in the company decision problem can be found in section 1.4.5 and Table 2. In this section **the ERG deemed the thresholds reported by the company to be appropriate based upon current NICE guidelines**. Results from the subgroup analyses for the key ORION trials are presented in section B.2.7 of the CS (page 99). The CS presents forest plots for each of the ORION trials of the subgroup analyses for differences in percentage change in LDL-C from baseline to Day 510 using MMRM and for differences in time-adjusted LDL-C between Day 90 and Day 540 using control-based PMM. There were no statistically significant differences between subgroups except for baseline LDL-C levels in the ASCVD population. The results sections on the subgroup analyses with regards to costs can be found in sections 3.4 and 2.10.5.2.

2.3 *Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

In the absence of head-to-head RCT evidence comparing inclisiran with active relevant comparators specified in the final scope of the National Institute for Health and Care Excellence (NICE), the company undertook a network meta-analysis (NMA) using the

placebo arm as an anchor (i.e., common comparator) to assess the relative clinical effectiveness and safety of inclisiran vs. alirocumab, evolocumab, or ezetimibe.

2.3.1 Inclisiran comparator studies

The company identified four studies where inclisiran was assessed that were relevant to the decision problem: ORION-9, ORION-10, ORION-11 and ORION-1.

ORION-9, -10 and -11 were part of the clinical effectiveness evidence submissed as part of the company submission and critiqued as part of the ERG report. ORION-9 was included in the NMA as part of the HeFH network.

Data from ORION-10 and ORION-11 were pooled due to the similarity in patient demographic characteristics, baseline LDL-C levels and methodology. The ERG agrees with the company regarding the similarly in methodology and baseline characteristics of patients in ORION-10 and ORION-11. Furthermore, ORION-10 and ORION-11 were undertaken around the same time. However, as **ORION-10 was conducted exclusively in the USA and ORION-11 was conducted in 8 different countries, it is possible that population-level differences exist in terms of geographic region.** To assess if this had a significant impact on the results, sensitivity analyses could have been performed which did not pool ORION-10 and ORION-11 and then judging how these results differed from the pooled analysis.

ORION-1 was a phase II trial included in the sensitivity analyses of the NMA. It was not part of the base case NMA , and the company did not include this trial as part of the clinical evidence for inclisiran, as stated in the CS Table 5. The relevant arms of this trial were the 300 mg inclisiran (n=61) and placebo (n=62) arms in the two-dose group.

2.3.2 Comparator studies

[redacted]The company provided a table of all NMAs and SRs which they reference checked for trials relevant for inclusion (appendix D, table 12). The ERG checked all studies from 2019 and 2020 identified within the company's NMA and SR list. The ERG found one reference not checked by the company, however believes it would be ineligible for inclusion due to being undertaken in the wrong population.[25] [redacted]

[redacted]

2.3.2.1 Alirocumab

[redacted]

2.3.2.2 Evolucumab

[redacted]

2.3.2.3 Ezetimibe

[redacted]

2.3.2.4 Other comparators

[redacted]

2.3.2.5 Company's feasibility assessment

[redacted]

[redacted]

Population

All relevant risk factors were considered within the ORION trials. However, only the ORION 11 trial included patients from the UK. There were 23 UK sites and 462 UK patients (CS table 10, page 58) all with ASCVD or ASCVD risk factors. Therefore, the results from the ORION-9 and ORION-10 trials may not generalise to UK patients. ORION-9 also did not include patients with a history of HeFH without ASCVD so the results may not generalise to this population.

[redacted]

Treatment

[redacted]

Outcome

[redacted]

Included and excluded studies

[redacted]

[redacted]

Quality assessment

[redacted]

[redacted]

Analysis

[redacted]

[redacted]

The ERG believes the methods used for the NMA are appropriate.

Table 13: Study design of studies excluded from the company NMA with reasons of exclusion

Study Name	Blinding	Phase	Treatment groups	Key Eligibility Criteria	Reason for exclusion	Countries	Primary outcome(s), and LDL-C related results
RUTHERFORD	Double-blind	2	AMG 145 350 mg SC Q4W AMG 145 420 mg SC Q4W Placebo SC Q4W	Aged 18 to 75 years LDL-C ≥ 2.6 mmol/L with triglycerides ≤ 4.5 mmol/L despite at least 4 weeks of stable statin or LLT before screening	"Evolocumab does not of interest" The dose required for comparison was 140 mg (Q2W), which the doses in this study were greater than	24 sites in North America, Western Europe, Hong Kong, Singapore. and South Africa	Percentage change in LDL-C from baseline to 12 weeks: 350 mg: -42.7 (-48.4, -37.0) 420 mg -50.7 (-60.9, -49.5) Placebo: 0.1 (-0.1, 0.3)
GAUSS	Double-blind	2	AMG 145 280 mg SC Q4W AMG 145 350 mg SC Q4W AMG 145 420 mg SC Q4W AMG 145 420 mg SC Q4W + ezetimibe 10 mg QD Placebo SC Q4W + ezetimibe 10 mg QD	Aged 18 to 75 years Patients with hypercholesterolaemia who were considered statin intolerant	"Evolocumab does not of interest" The dose required for comparison was 140 mg (Q2W), which the doses in this study were greater than, except for the AMG 145 280 mg SC Q4W group	33 sites in North America, Australia, and Europe	Percentage change in LDL-C from baseline to 12 weeks: 280 mg: -40.8 (-48.6, -32.9) 350 mg: -42.6 (-50.5, -34.7) 420 mg -50.7 (-58.6, -42.8) 420 mg + E: -63.0 (-71.4, 54.5) Placebo: -14.8 (-22.6, -7.0)
GAUSS-3	Double-blind		Phase A: Atorvastatin 20 mg Placebo Phase B: Evolocumab 420 mg SC QM + Placebo oral QD Ezetimibe 10 mg oral QD + Placebo SC QM	Aged 18 to 80 Inability to tolerate atorvastatin at 10 mg and any other statin at any dose or 3+ statins with 1 at the lowest average daily starting dose and 2 other statins at any dose	"Evolocumab does not of interest" The dose required for comparison was 140 mg (Q2W), which the doses in this study were greater than		Percentage change in LDL-C from baseline to mean of 22 and 24 weeks: Evolocumab: -54.5 (-57.2, -51.8) Ezetimibe: -16.7 (-20.5, -12.9) Percentage change from baseline to week 24: Evolocumab: -52.8 (-55.8, -49.8) Ezetimibe: -16.7 (-20.8, -

							12.5)
ORION-1*	Double-blind	2	Single-dose Inclisiran 200 mg SC Inclisiran 300 mg SC Inclisiran 500 mg SC Placebo SC Double-dose Inclisiran 100 mg SC Inclisiran 200 mg SC Inclisiran 300 mg SC Placebo SC	Aged ≥ 18 years LDL-C ≥ 70 mg/dL if ASCVD history, LDL-C ≥ 100 mg/dL otherwise Receiving maximum possible dose of a statin with or without LLT at stable dose for at least 30 days prior to screening	"35% not receiving high intensity statin at baseline; 25% on ezetimibe" In Ray 2017, the first paragraph of results reported 273% of patients were receiving statin therapy, and 31& of the patients were receiving ezetimibe". High intensity statin use ranged from 33% to 52% in the various groups, and ezetimibe use ranged from 25% to 38% (from supplementary appendix 5.9 Table S2)	54 sites in North America, The Netherlands, UK, and Germany	Change in LDL-C from baseline to Day 180 Single: Inclisiran 200 mg: -27.9 (-33.1, -22.7) Single: Inclisiran 300 mg: -38.4 (-43.6, 33.2) Single: Inclisiran 500 mg: -41.9 (-47.2, -36.7) Single: Placebo: 2.1 (-2.9, 7.2) Double: Inclisiran 100 mg: -35.5 (-40.0, -31.0) Double: Inclisiran 200 mg: -44.9 (-49.3, -40.4) Double: Inclisiran 300 mg: -52.6 (-57.1, -48.1) Double: Placebo: 1.8 (-2.6, 6.3)
ODYSSEY OPTIONS I	Double-blind	3	Entry: Atorvastatin (ATV) 20 mg Alirocumab 75/150 mg SC Q2W + ATV 20 mg Ezetimibe 10 mg oral QD + ATV 20 mg Atorvastatin 40 mg Entry: Atorvastatin 40 mg Alirocumab 75/150 mg SC Q2W + ATV 20 mg	Aged 18 years or older Very high risk of CVD LDL-C ≥ 70 mg/dL LDL-C ≥ 100 mg/dL and high CVD risk	"Atorvastatin does was doubled in statin only group"	85 sites in Australia, Canada, France. Germany. Italy. Mexico, Spain, UK, USA	Percentage change in LDL-C from baseline to 24 weeks: Entry: Atorvastatin (ATV) 20 mg Alirocumab 75/150 mg: -44.1 (-52.9, -35.3) Ezetimibe 10 mg: -20.5 (-29.7, 11.3) Atorvastatin 40 mg: -5.0 (-14.0, 4.0). Entry: Atorvastatin 40 mg Alirocumab 75/150 mg: -54.0 (-62.4, -45.6)

			Ezetimibe 10 mg oral QD + ATV 40 mg Atorvastatin 80 mg Rosuvastatin 40 mg				Ezetimibe 10 mg: -22.6 (-31.0, -14.2) Atorvastatin 80 mg: -4.8 (-13.0, 3.4) Rosuvastatin 40 mg: -21.4 (-29.6, 13.2)
ODYSSEY OPTIONS II	Double-blind	3	Entry: Rosuvastatin (RSV) 10 mg Alirocumab 75 mg SC Q2W + RSV 10 mg Ezetimibe 10 mg oral QD + RSV 10 mg Rosuvastatin 20 mg Entry: Rosuvastatin 20 mg Alirocumab 75 mg SC Q2W + RSV 20 mg Ezetimibe 10 mg oral QD + RSV 20 mg Rosuvastatin 40 mg	Adult patients with hypercholesterolemia at very-high or high CS risk receiving rosuvastatin 10 or 20 mg/day for at least 4 weeks prior to screening	"Rosuvastatin does was doubled in statin only group"	79 sites in Australia, Germany, Italy, Spain, UK, Mexico, USA, and Canada	Percentage change in LDL-C from baseline to 24 weeks: Entry: Rosuvastatin (RSV) 10 mg Alirocumab 75mg: -50.6 (-58.8, 42.4) Ezetimibe 10 mg: -14.4 (-23.0, -5.8) Rosuvastatin 20 mg: -16.3 (-24.3, -8.3) Entry: Rosuvastatin 20 mg Alirocumab 75 mg: -36.3 (-50.2, -22.4) Ezetimibe 10 mg: -11.0 (-25.1, 3.1) Rosuvastatin 40 mg: 15.9 (-29.8, -2.0)
DESCARTED	Double-blind	3	Evolocumab 420 mg SC Q4W Placebo SC Q4W Split between 4 groups: Diet alone Diet + Atorvastatin 10 mg Diet + Atorvastatin 80 mg	Aged 18 to 75 years LDL-C ≥ 75 mg/dL Fasting triglycerides ≤ 4.52 mmol/L	"Evolocumab does not of interest" The dose required for comparison was 140 mg (Q2W), which the doses in this study were greater than	88 centres in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Hungary, South Africa,	Percentage change in LDL-C from baseline to 52 weeks: Diet alone: Evolocumab: -51.5 (-52.0, -50.1) Placebo: 4.2 (3.1, 5.3) Diet + ATV 10 mg: Evolocumab: -54.7 (-54.9, -54.5)

			Diet + Atorvastatin 80 mg + Ezetimibe 10 mg			USA (9 countries)	Placebo: 6.9 (6.5, 7.3) Diet + ATV 80 mg: Evolocumab: -46.7 (-47.2, -46.2) Placebo: 10.1 (9.1, 11.1) Diet + ATV 80 mg + Ezetimibe 10 mg: Evolocumab: -46.8 (-47.3, -46.3) Placebo: 1.7 (0.6, 2.8) All patients: Evolocumab: -50.1 (-50.2, -50.0) Placebo: 6.8 (6.6, 7.0)
ODYSSEY Japan	Double-blind	3	Alirocumab 75 mg SC Q2W Placebo SC Q2W	Adults with heFH with or without a history of documented CAD, or patients with non-FH at high CVD risk with a history of documented CAD, or classified JAS category III Required to have hypercholesterolaemia that was not adequately controlled despite taking a stable daily dose of statin therapy with or without LLT	"Low-moderate dose statins" Background statin therapy at randomisation included: Pravastatin 5-20 mg Rosuvastatin 2.5-20 mg Atorvastatin 5-40 mg Pitavastatin 0.5-4 mg Simvastatin 5-10 mg Fluvastatin 20-30 mg In ORION-9 and ORION-11, over 70% of patients had high-intensity statin use at baseline, in ORION-10 this was in the 67-68%.	31 sites in Japan	Percentage change in LDL-C from baseline to 24 weeks: Alirocumab: -62.5 (-62.7, -62.3) Placebo: 1.6 (1.2, 2.0)
EASEGO	Blinded		Ezetimibe 10 mg oral QD +	Aged 18 years or older Stable Type II diabetes	"Atorvastatin or simvastatin dose was	21 cardiology clinics in The	Percentage of patients reaching LDL-C targets

	endpoint		simvastatin 20 mg oral QD Double statin dose	and/or established CDH LDL-C between 2.5 and 4.99 mmol/L despite treatment with ATV 10 mg or simvastatin 20 mg	doubled"	Netherlands	Target LDL-C = 2.5 mmol/L or lower: Ezetimibe + simvastatin: 119 (67%) Double statin: 49 (26%) OR = 5.7 (3.7, 9.0) Target LDL-C = 2.0 mmol/L or lower: Ezetimibe + simvastatin: 53 (30%) Double statin: 6 (3%) OR = 12.9 (5.4, 31.0)
YUKAWA	Double-blind	2	Evolocumab 70 mg SC Q2W Evolocumab 140 mg SC Q2W Placebo SC Q2W Evolocumab 280 mg SC QM Evolocumab 420 mg SC QM Placebo SC QM	Aged 20 to 80 years Classified high-risk for CVD events	"Low-moderate intensity statins" Only 19 (6.2%) patients were on high-intensity statins using the global definition, or 73 (23.8%) patients using the Japan-specific definition	42 sites in Japan	Percentage change in LDL-C from baseline to 12 weeks: Evolocumab 70 mg: -52.9 (-53.7, -52.1) Evolocumab 140 mg: -68.6 (-69.4, -67.8) Placebo Q2W: NA Evolocumab 280 mg: -58.2 (-59.1, -57.3) Evolocumab 420 mg: -63.9 (-64.8, -63.0) Placebo QM: NA
YUKAWA-2	Double-blind	3	Evolocumab 140 mg SC Q2W Placebo SC Q2W Evolocumab 420 mg SC QM Placebo SC QM	Aged 20 to 80 years High risk for CV events based on JAS criteria On a stable dose of an approved statin within 4 weeks prior to LDL-C screening without need for up-titration Use of LLT had to be unchanged within 4 weeks prior to screening	"Low-moderate intensity statins" "Patients were then randomized 1:1 to 1 of 2 atorvastatin treatment groups consistent with low (5 mg/day) and high (20 mg/day) statin doses used in clinical practice in participating regions"	Japan	Percentage change in LDL-C from baseline to mean of 10 and 12 weeks: Evolocumab Q2W + ATV 5 mg: Evolocumab QM + ATV 5 mg: Evolocumab Q2W + ATV 20 mg: Evolocumab QM + ATV 20 mg: Percentage change from baseline to week 12:

					to complete a 4-week lipid stabilisation period prior to randomisation		Evolocumab Q2W + ATV 5 mg: -74.9 (-80.2, -69.6) Evolocumab QM + ATV 5 mg: -69.9 (-74.6, -65.2) Evolocumab Q2W + ATV 20 mg: -75.9 (-83.5, -68.3) Evolocumab QM + ATV 20 mg: -66.9 (-72.8, -61.0)
Luo (216)	Double-blind		Ezetimibe 10 mg oral QD Atorvastatin 20 mg oral QD Atorvastatin 20 mg oral QD	CHD patients with carotid atherosclerosis	"Low baseline LDL-C" Baseline LDL-C in the combination group was 3.57 ± 0.38 mmol/l and in the control group it was 3.52 ± 0.46 mmol/l, compared to 4 mmol/l in ORION-9, and 2.7 mmol/l in both ORION-10 and ORION-11		Mean change in blood lipids before and after treatment Post-treatment LDL-C: Combination group: 2.12 ± 0.58 Control: 2.63 ± 0.56
Nakamura (2012)	Double-blind		Ezetimibe 10 mg QD plus statin Double ongoing statin dose	Remnant-like lipoprotein particle cholesterol levels ≥ 5.0 mg LDL-C ≥100 mg/dL at screening Aged 35–75 years Angiographic documentation of an organic stenosis of ≥ 75% of ≥ 1 major coronary artery.	"Double-dose statin arm"	Japan	Percentage change in RLP-C from baseline after 6 months Change in LDL-C: Statin + ezetimibe: -24.2 ± 23.2* Double statin dose: -20.9 ± 18.7* * Does not specify if this is SD or SE

2.4 *Critique of the indirect comparison and/or multiple treatment comparison*

The NMA base case results are presented in Table 14 and explained in the following sections.

2.4.1 ASCVD and PPER on MTD Statins population

[redacted]

2.4.2 ASCVD and ASCVD PPER intolerant to Statins

[redacted]

[redacted]

2.4.3 HeFH population

[redacted]

[redacted]

[redacted]e.

Table 14: NMA base case results

	ASCVD MTD		ASCVD intolerant		HeFH MTD	
Inclisiran vs	**Mean difference (95% CrI)**	**Probability (inclisiran better than comparator)**	**Mean difference (95% CrI)**	**Probability (inclisiran better than comparator)**	**Mean difference (95% CrI)**	**Probability (inclisiran better than comparator)**
Percentage change in LDL-C at 24 weeks						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolucumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute change in LDL-C at 24 weeks						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolucumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total discontinuations at ≥24 weeks*						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolucumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations due to AEs*						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolucumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage change in HDL-C at 24 weeks						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolucumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ezetimibe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Outcome is Random-effect odds ratio (95% CrI)
Abbreviations: AE = adverse events; ASCVD = Atherosclerotic Cardiovascular Disease; CrI = credible interval; HeFH = Heterozygous Familial hypercholesterolaemia; HDL-C = High Density Lipoprotein Cholesterol; LDL-C = Low Density Lipoprotein Cholesterol; MTD = Maximum Tolerated Dose; NA = not applicable

2.5 *Summary of the network meta-analysis (NMA)*

[redacted]

The methodology and results of the NMA are presented in section 2.4 of the Evidence Review Group (ERG) report. The ERG checked to verify the adequacy and validity of the company's approach in assessing feasibility of NMA, treatment network connectivity, heterogeneity assumption (for direct pair-wise meta-analysis), and transitivity-consistency assumption (for NMA). For this purpose, the ERG report provides Tables 1-6, which are presented below.

2.5.1 ERG critique of assessment of feasibility of NMA

[redacted] eligible RCTs evaluating the efficacy and safety of inclisiran as well as specific treatment comparators (i.e., alirocumab, evolocumab, ezetimibe, and placebo) along with outcomes of interest were included in the feasibility assessment for conducting an NMA.

The company assessed the feasibility of NMA by examining

- The treatment network connectivity
- Heterogeneity (for direct pair-wise meta-analysis)
- Transitivity-consistency assumption (for NMA)

For the purpose of assessing and addressing the transitivity-consistency assumption, the company selected the following potential effect modifiers *a priori*: trial design/methodology (e.g., randomisation, blinding), baseline population characteristics (e.g., LDL-C as an inclusion criteria/mean baseline value, background statin/ezetimibe use, cardiovascular risk), treatment characteristics (dose/schedule and mode of administration of active treatments and placebo), and outcome characteristics (time points of assessment).

The ERG considers the company's overall approach for assessing the feasibility of NMA to be appropriate, as it conforms the existing NMA recommendations.[34-37]

2.5.2 ERG critique of treatment network connectivity of NMA

The network connectivity was examined through the characteristics of treatments (dose, regimen, and schedule) and outcomes (definitions and assessment time) (Document B, Section B2.9, page 110). Although separate NMA models in three subgroups of participants were feasible (ASCVD/PPER on MTD statins, ASCVD/PPER intolerant to statins, and HeFH on MTD of statins), no NMA was feasible for the subgroup of HeFH participants intolerant to statins, since none of the comparator studies for this group reported the outcome(s) of interest (Document B, Figures 27-29).

The treatment types, doses, and schedules in the ORION and comparator studies were sufficiently comparable in order to connect the treatment nodes (the ERG report, Table 1 and Table 2). The ORION studies used the same regimen/dose (285-300 mg) of inclisiran. Alirocumab in most of the studies included in NMA was administered at 75 mg up titrated to 150 mg Q2W SC. Four studies, 2 in each separate network, administered 150 mg Q2W SC of alirocumab (ODYSSEY LONG TERM, NCT01288443, ODYSSEY HIGH FH, NCT01266876).[30, 38-40] In all studies (except FOURIER),[41] evolocumab was administered at 140 mg Q2W SC. In FOURIER study, evolocumab was given in two different regimens either 140 mg Q2W SC or 420 QM SC. In all trials ezetimibe was given at 10 mg QD orally. Overall, there were no major differences in the active treatments across the trials included in NMA. In most studies, placebo was administered subcutaneously twice a week. In ORION-10/11 studies,[17] placebo was administered subcutaneously on day 1, day 90, and once in 6 months thereafter.

The ERG notes that the treatment nodes were connected correctly in the three NMA plots.

2.5.3 ERG critique of assessment of heterogeneity (for direct pair-wise meta-analysis)

[redacted]

[redacted]

The ERG visually inspected forest plots of direct meta-analyses (base case scenarios) comparing active treatments to placebo (Document B, Figure 31, Figure 41, and Figure 51, pages 117-135) and did not note clinically appreciable variability between the effect estimates for percent change in LDL-C for individual studies across three distinct populations.

It would be more informative if the company conducted a subgroup analysis of the trials to explore if certain pre-defined factors (e.g., age, proportion of people intolerant to statins, ASCVD status, mean baseline LDL-C) were differentially distributed across the studies pooled in direct meta-analyses. For example, ORION-10 included only ASCVD population (secondary prevention), whereas ORION-11 included the mix of ASCVD (87.4%) and PPER populations (12.5%). Moreover, the proportion of people intolerant to statins differed between the two trials (22.0% vs. 11.4%, respectively). One might expect that these cross-trial differences (and other unobserved factors independently associated with CV risk) could have contributed to the observed variation and heterogeneity in the direct meta-analyses comparing active treatments to placebo in ASCVD and/or PPER populations on MTD of statins.

[redacted]

2.5.4 ERG critique of assessment of transitivity assumption (for NMA)

The company assessed and addressed transitivity assumption using two approaches: a) subgroup analysis and b) base case and sensitivity analysis (Appendix D, Section D2, page 110).

For subgroup analysis, the company constructed three NMAs in three distinct populations (Document B, Figures 27-29, and pages 115-116): a) ASCVD with or without PPER on MTD of statins, b) ASCVD with or without PPER intolerant to statins, and c) HeFH on MTD of statins (ASCVD and/or PPER).

For base case and sensitivity analysis, the company formulated assumptions and corresponding recommendations to operationalize the NMA conduct in terms of adjusting for differences in the distribution of the *a priori* selected effect modifiers. This approach also allowed to explore the impact of these effect modifiers on NMA results through base case and sensitivity scenarios (Table 15 and Table 16).

The ERG examined and commented on the appropriateness of the company's subgroup and sensitivity analyses (Table 15). Furthermore, the ERG conducted a qualitative examination of the distribution of potential effect modifiers (e.g., trial design/methodology, patient baseline demographics, background statins/ezetimibe, mean LDL-C as an inclusion criteria or baseline value) across the network(s) of studies (Table 16 to Table 20).

Briefly, the sensitivity analysis focused on the robustness of NMA mean effect estimates for percent and absolute change in LDL-C at [redacted]. Several scenarios were conducted by adding data from ORION-1 study (outlier in terms of ezetimibe use and 27% of patients intolerant to statins) and data with time-points of outcome assessment from ORION-10/11 trials (e.g., time-adjusted or 90-day data). Other scenarios excluded data with specific subgroups (e.g., intolerant to statins in ORION 9/10/11 studies) or excluded outlier studies in terms of the outcome measurement methodology (ODYSSEY OUTCOMES) [14] and inclusion criteria (LDL-C ≥160 mg/dL in ODYSSEY HIGH FH).[39]

More details on the company's approaches for addressing the transitivity assumption and effect modifiers in the sensitivity analysis are provided in Table 15 and Table 16. The ERG assessment/comment regarding each issue is provided in Table 15.

Table 15. The company's assumptions regarding effect modifiers used in the assessment of the NMA feasibility

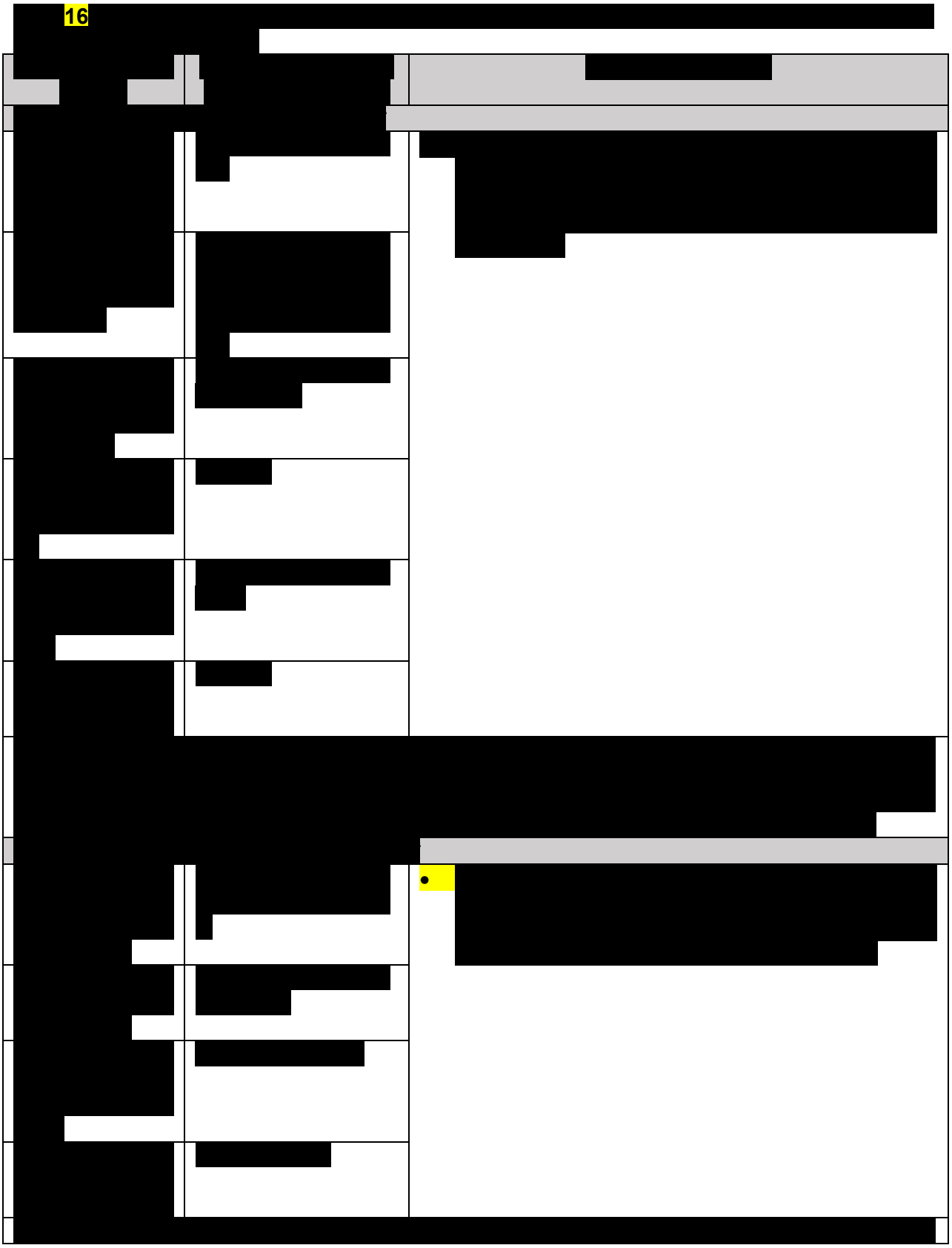
Effect modifiers	The company's and ERG comments
Population characteristics	
Background Ezetimibe	**The company's assumptions and recommendations:** Perform analyses without consideration of background ezetimibe as an effect modifier. Subgroup data for % change in LDL-C presented by two of the included trials (ODYSSEY Long Term [alirocumab vs. placebo][30] and LAPLACE-TIMI 57 [evolocumab vs. placebo][32]) did not suggest background/baseline ezetimibe use to be a treatment-effect modifier.
	ERG comments: In order to corroborate or refute this finding, the ERG examined if the use of background ezetimibe influenced the magnitude of percent change in LDL-C in other studies. Unfortunately, none of the studies (except for one - RUTHERFORD-2 study)[45] reported a subgroup analysis by ezetimibe use for various reasons (e.g., ezetimibe use not reported, no ezetimibe use, small proportion of ezetimibe use) or no reason. The subgroup analysis in RUTHERFORD-2 study showed that there was no difference in the percent change of LDL-C for evolocumab vs. placebo between ezetimibe users and non-users. This observation corroborated the company's finding that background ezetimibe did not modify the magnitude of benefit (i.e., percent reduction in LDL-C). The ERG agrees with the company that background ezetimibe use should not be considered as an effect modifier.
Background Statins	**The company's assumptions and recommendation:** Separate analyses were performed for trials where patients were receiving MTD statins and those in patients who are statin intolerant. Imbalances in doses of background therapy across treatment comparisons such as double-dose statins were assumed to bias the NMA and impact the relative treatment effects. The company stated that several RCTs were excluded from NMA due to having non-similar distribution of the background statin use (e.g., double-dose, low-moderate intensity) to other trials included in the NMA which used MTD of statin (Appendix D, 2.2.3 Background Statins, page 118) (ODYSSEY JAPAN, YUKAWA, YUKAWA-2, ODYSSEY OPTIONS I, ODYSSEY OPTIONS II, EASEGO, Nakamura 2012, and ORION-1).[46-54] It was assumed that individual statins (e.g., atorvastatin, rosuvastatin, simvastatin) would have similar efficacy as background therapy, regardless of the specific statin and dosage. the ORION-1 trial (Phase II study)[54] of ASCVD patients receiving MTD statins was considered an outlier in terms of the higher proportion of patients intolerant to statins (27%) compared to ORION-10 (22%) and

	ORION-11 (12%) trials. Therefore, this study was not included in base case NMA, but only in a sensitivity analysis. The full ITT population (on MTD statins) from the ORION trials is used for the base-case analysis. Note that small proportion of statin intolerant patients in the ORION trials (ORION-10 [22%], ORION-11 [12%], and ORION-9 [25%]) would not bias the NMA. The sensitivity analysis of NMA excluded data on statin intolerant patient subgroups from ORION-10 and ORION-11. The NMA results (for percent change of LDL-C) after this exclusion remained consistent in magnitude and certainty with those of the base case. Analysis based on statin intolerant populations included data only on statin intolerant subgroups from ORION-10 and ORION-11 studies.[17]
	ERG comments: The ERG agrees with the assumptions and recommendation to exclude studies with background statin use other than MTD.
CV risk	**The company's assumptions and recommendations:** For the base-case analyses, it was assumed that differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) would not impact the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations. Given the inconsistent and limited reporting of baseline characteristics related to CV risk, and that the largest network included 11 trials, meta-regression was not feasible. A subgroup analysis based on baseline LDL-C was not recommended either, given the limited number of trials reporting this data and the sample size of the subgroups. ODYSSEY HIGH FH[39] was identified as an outlier among trials of patients with HeFH, given the inclusion criteria (LDL-C ≥160 mg/dL) and observed mean baseline LDL-C (196.3-201 mg/dL), which were higher than in comparator trials. This difference is believed to have resulted in a lower reduction in LDL-C relative to placebo. Therefore, it was recommended to exclude this trial during the sensitivity analysis of NMA. ODYSSEY OUTCOMES[14] was also deemed an outlier amongst trials of ASCVD patients receiving MTD statins. In this trial, the median time since a recent acute coronary event was 2.6 months, which, based on clinical expert feedback, may result in highly variable LDL-C values at baseline due to plaque rupture, and subsequently unreliable results. A sensitivity analysis excluding this trial was recommended.
	ERG comments: Inconsistent definitions of ASCVD PPER risk between the ORION and other studies may have resulted in differences in the distribution of CV risk across the networks of studies. The ERG team believes this would likely compromise the transitivity assumption to some degree. Most studies included either participants with history of CV (ASCVD) event, those with risk equivalent (ASCVD-RE or PPER), or both groups. In addition, studies used inconsistent definitions and criteria for categorizing CV risk. Inevitably, this may have led to some variability in the distribution of

	CV risk across the trials in NMA. This limitation in evidence complicates any type of comparison for CV risk. The inconsistency in definitions and poor reporting coupled with small number of studies included in NMA precluded the conduct of meta-regression or subgroup analysis that would help assess reliably the impact of CV risk on the NMA outcomes of interest as well as adjust for a potential bias due to non-uniform distribution of CV risk across the network of studies.
Other factors related CV risk	**ERG comments:** The ERG noted that in NMA of ASCVD/PPER MTD of statins (mostly non-HeFH population), one study (ODYSSEY LONG TERM) included 17.7% participants with HeFH. The effect estimate (MD in percent change of LDL-C) in the NMA was used based on ITT population (−61.9%) instead of the subgroup of non-HeFH population. However, the ERG confirmed that the effect estimates in non-HeFH and HeFH populations were similar (-61.5% vs. -63.2%, respectively).
Treatment characteristics	
Inclisiran	**The company's assumptions and recommendations:** No differences were observed between ORION trials with respect to inclisiran doses. No trials were excluded from the analyses based on Inclisiran dosing.
	ERG comments: The ERG agrees with this recommendation.
Alirocumab	**The company's assumptions and recommendations:** It was assumed that alirocumab 75mg Q2W up titrated to 150 mg if required and alirocumab 150 mg Q2W regimens were appropriate to be considered as the same treatment in the analysis. Given the widespread availability of the 75 mg dose, this regimen was included.
	ERG comments: The ERG notes that there were 2 trials in each of the two networks that used 150 mg Q2W regimens (without titration). The ERG does not believe that a difference in the effect of alirocumab titrated from 75mg to 150 mg Q2W vs. 150 mg Q2W would bias the NMA findings. ASCVD-PPER on MTD of statins: ODYSSEY LONG TERM, NCT01288443 HeFH on MTD of statins: ODYSSEY HIGH FH, NCT01266876
Evolocumab	**The company's assumptions and recommendations:** FOURIER administered two different regimens of evolocumab: 140 mg Q2W or 420 mg QM, with treatment allocation based on patient preference (10.1% were receiving the QM dose). The FOURIER authors reported data on pooled both doses compared to matched placebo.
	ERG comments: The magnitude of benefit of evolocumab in FOURIER study was consistent across levels of intensity of statin therapy, regardless of ezetimibe use, and with both the dosing regimen of 140 mg every 2 weeks and that of 420 mg monthly.
Ezetimibe	**The company's assumptions and recommendations:** Six trials assessed ezetimibe as a comparator, three of which were in MTD-statin group (ODYSSEY COMBO II, [55] ODYSSEY EAST[29] and LAPLACE-2) and three in statin-intolerant patients (ODYSSEY ALTERNATIVE,[56] GAUSS-2,[57] and Gauss-4[58]).

	All trials assessed the same dosing regimen of 10 mg once daily (OD) and were included in the analysis. No assumptions needed; No trials were excluded from the analyses.
	ERG comments: The ERG considers this recommendation to be appropriate.
Placebo	**The company's assumptions and recommendations:** Imbalances in doses of background therapy across treatment comparisons such as double-dose statins were assumed to bias the NMA and impact the relative treatment effects. 4 trials were excluded from the analysis wherein patients randomised to the placebo arm received double-dose statins (ODYSSEY OPTIONS I, ODYSSEY OPTIONS II, EASEGO, and Nakamura 2012.[53]
	ERG comments: All studies with populations taking statins that were included in the 2 NMAs were selected so that statin intake was at MTD. The company excluded several RCTs from NMA due to their having non-similar distribution of the background statin use (e.g., low-moderate, or low intensity) to other trials in the NMA which used MTD of statin (ODYSSEY JAPAN, YUKAWA, YUKAWA-2). Moreover, the company excluded all studies using double-dose statins as background treatment (ODYSSEY OPTIONS I, ODYSSEY OPTIONS II, EASEGO, Nakamura 2012). In such studies placebo arms would be potentiated with the addition of double-dose statins relative to placebo arms of other studies where double-dose statins were not used. The ERG believes that the above-mentioned decisions would contribute to more uniformity of placebo arms of studies included in the NMAs. In most studies, placebo was administered subcutaneously twice a week. ORION-10/11 studies placebo was administered subcutaneously on day 1, day 90, and once in 6 months thereafter.
Outcome Characteristics	
Time points of assessment	**The company's assumptions and recommendations:** Although total study follow-up of the ORION trials was 540 days (approximately 77 weeks), several PCSK9 inhibitor trials had a much shorter duration of follow-up (i.e., 12-week follow-up for the GAUSS trials, RUTHERFORD-2, LAPLACE-TIMI 57 and 24-week follow-up for ODYSSEY ALTERNATIVE). With regards to efficacy outcomes of interest, the most commonly reported time points were 12 or 24 weeks; which closely align with the 90-day and 150-day outcomes reported by the ORION trials. Visual inspection of the graphical results of LDL-C for ORION and comparator trials shows a plateau in percent change in LDL-C over time, with relative treatment effects decreasing slightly in most studies. Given the observed plateau, the fact that up-titration of alirocumab typically occurred at week 12, and the fact that most studies reported efficacy outcomes of interest at 24 weeks (with the exception of several evolocumab trials), 24

	weeks (or 150 days for inclisiran) was selected as the preferred time-point of interest for the base-case. The 12-week data was included only when 24-week data was not reported. It is assumed that at 24 weeks as the target time point of interest, optimal efficacy will have been reached for all treatments, particularly alirocumab which may have been up-titrated from 75 mg to 150 mg at week 12. Several SAs were performed to test the impact of time point selection from the ORION trials, including a scenario which includes the results at 90 days, and another that includes time-adjusted results, which excludes the 90-day results from change measurements.
	ERG comments: The ERG agrees with these assumptions and recommendations.
Safety endpoints	**The company's assumptions and recommendations:** For safety outcomes of interest, given the variation in follow-up, end of study outcomes were considered comparable if the duration of follow-up was 24 weeks or longer. Trials with total study duration shorter than 24 weeks were excluded from the analyses for treatment discontinuations.
	ERG comments: The ERG agrees with these assumptions and recommendations.
PCSK9=proprotein convertase subtilisin kexin 9; SA=sensitivity analysis; ERG=evidence review group; SA=sensitivity analysis; ASCVD=atherosclerotic cardiovascular disease; PPER=primary prevention with elevated risk; MTD=maximally tolerated dose; NMA=network meta-analysis; HeFH=heterozygous familial hypercholesterolaemia; SC=subcutaneous; Q2W=every 2 weeks; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; CV=cardiovascular	



* Studies underlined used Alirocumab 150mg Q2W
[µ] FOURIER study administered two different regimens of evolocumab (140 mg Q2W or 420 mg QM)

17

Study name	Key eligibility criteria
Population: ASCVD with or without PPER on MTD of statins	

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ASCVD= atherosclerotic cardiovascular disease; ASCVD-RE= atherosclerotic cardiovascular disease-risk equivalent; PPER=primary prevention with elevated risk; MTD=maximally tolerated dose; LLT=lipid lowering treatment; CHD=coronary heart disease, PAD=peripheral arterial disease; T2D=type 2 diabetes; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; JAS= Japan Atherosclerosis Society; NCEP-ATP= National Cholesterol Education Program-Adult Treatment Panel III goal; HeFH= heterozygous familial hypercholesterolemia

[redacted] 18 [redacted]

Study name	Trial design	Sample size N	Treatment	Male (%)	Mean Age (yrs)	LDL-C inclusion criteria (mg/dL)	Baseline mean LDL-C (mg/dL)	ASCVD (%)	CHD (%)	ASCVD RE (%)	Ezetimibe background (%)	Intolerant to statin (%)
[redacted]												

Study name	Trial design	Sample size N	Treatment	Male (%)	Mean Age (yrs)	LDL-C inclusion criteria (mg/dL)	Baseline mean LDL-C (mg/dL)	ASCVD (%)	CHD (%)	ASCVD RE (%)	Ezetimibe background (%)	Intolerant to statin (%)

PC=placebo-controlled; DB=double blind; ASCVD= atherosclerotic cardiovascular disease; ASCVD-RE= atherosclerotic cardiovascular disease-risk equivalent; PPER=primary prevention with elevated risk; MTD=maximally tolerated dose; LDL-C=low-density lipoprotein cholesterol; CHD=coronary heart disease; PC=placebo controlled; RE=risk equivalent; yrs=years; NR=not reported; AC=active-controlled

[redacted] 19 [redacted]

Study name	Trial design	Sample size N	Treatment	Male (%)	Mean Age (yrs)	LDL-C inclusion criteria (mg/dL)	Baseline mean LDL-C (mg/dL)	ASCVD (%)	CHD (%)	ASCVD RE (%)	Ezetimibe background (%)	Intolerant to statin (%)
[redacted]												
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Study name	Trial design	Sample size N	Treatment	Male (%)	Mean Age (yrs)	LDL-C inclusion criteria (mg/dL)	Baseline mean LDL-C (mg/dL)	ASCVD (%)	CHD (%)	ASCVD RE (%)	Ezetimibe background (%)	Intolerant to statin (%)
			[redacted]			[redacted]						
[redacted]												

[redacted] 20 [redacted]

Study name	Trial design	Sample size N	Treatment	Male (%)	Mean Age	LDL-C inclusion criteria (mg/dL)	Baseline mean LDL-C (mg/dL)	ASCVD (%)	CHD (%)	ASCVD RE (%)	Ezetimibe background (%)	Intolerant to statin (%)
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2.5.5 ERG critique of assessment of consistency assumption (for NMA)

The company assessed the consistency assumption by comparing the degree of agreement between the effect estimates of direct and indirect comparisons of the same two treatments for closed loops (Company's clarification response, question A20, page 32). Only two closed loops were present across the analysed networks, both of which found in the ASCVD and/or PPER population on MTD of statins network (Document B, Figure 27, page 115). One loop (loop #1) is located between placebo, evolocumab, and ezetimibe, and the other one (loop #2) between placebo, alirocumab, and ezetimibe.

The company assessed consistency by comparing the direct effects (mean percent change in LDL-C as reported in primary study) with the indirect effects based on random-effects (RE) Bucher indirect treatment comparison method and those estimated based on the RE NMA for the same pair-wise contrasts, as recommended by NICE.[59] More specifically, in loop #1 (placebo-evolocumab-ezetimibe) which is created by a single multi-arm trial (LAPLACE-2),[42] which had data on all three treatments in the loop and two LAPLACE-TIMI[32] and FOURIER trials,[41]

[redacted]

Loop #2 (placebo-alirocumab-ezetimibe) was created by independent sources of data from 9 trials (i.e. there were no three-armed studies contributing to this loop) (LAPLACE-2,[42] ODYSSEY OUTCOMES,[14] ODYSSEY KT,[26] ODYSSEY LONG TERM,[30] NCT01288443,[38] ODYSSEY CHOICE I,[43] ODYSSEY EAST,[29] ODYSSEY COMBO I,[28] ODYSSEY COMBO II[55]).

[redacted]

The ERG notes that the company did not provide similar consistency assessments for the remaining pair-wise comparisons in the two loops (placebo-evolocumab, evolocumab-ezetimibe, placebo-alirocumab, and alirocumab-ezetimibe). This information would allow the ERG to have a more comprehensive assessment and opinion on the consistency assumption in this NMA.

Overall, the ERG believes that the evidence of agreement between the direct and indirect estimates from closed loops provided by the company gives an additional assurance that the transitivity assumption was not gravely violated and that the effect modifiers were not distributed differentially across the network comparisons.

2.5.6 Summary and points of uncertainty

The methodology and results of the NMA are presented in Section 2.3 of the Evidence Review Group (ERG) report. With the exception of safety outcomes for ASCVD statin intolerant population, RE analyses were most appropriate given the number of studies per node and observed heterogeneity in patient/trial characteristics. Given that FE models include the strong (and unlikely to be true) assumption of homogeneity, RE analyses were used as the base case.

Overall, the **ERG considers that the company used adequate methodology to conduct the NMA** comparing inclisiran, alone or with a statin, with or without other lipid-lowering therapy to other therapies for the management of hypercholesterolemia in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or in patients who are statin-intolerant, or for whom a statin is contraindicated.

The company assessed the feasibility of NMA by examining treatment network connectivity, heterogeneity (for direct pair-wise meta-analysis), and transitivity-consistency assumption (for NMA). *A priori* selected effect modifiers known to potentially change the treatment effect, if differentially distributed, were also provided. The **ERG considers the company's overall approach for assessing the feasibility of NMA to be appropriate, as it conforms the existing NMA recommendations**.[34-37]

The ERG believes that the treatment nodes were connected correctly in the three NMA plots given the characteristics of treatments (dose, regimen, and schedule) and outcomes (definitions and assessment time). The treatment types, doses, and schedules in the ORION and comparator studies were sufficiently comparable in order to connect the treatment nodes. In most studies, placebo was administered subcutaneously twice a week.

The company conducted heterogeneity tests for direct meta-analyses of primary studies comparing the effects of active treatments vs. placebo in ASCVD and HeFH populations. The results of these tests were statistically significant, [redacted] The company noted that high I^2 does not necessarily imply important between-study differences and that may be influenced by small number of studies pooled, large sample sizes, and a small within-study sampling error. Usual recommendation is not to rely solely on the statistical tests when

exploring between-study heterogeneity, but rather to explore the treatment effect variation (and its causes) in terms of the units of clinical benefit via visual inspection of forest plots, subgroup analysis, or meta-regression. For example, even if the [redacted]

The ERG states that the company did not conduct a formal subgroup analysis to identify factor(s)/or study that contributed to statistical heterogeneity. The ERG visually inspected forest plots of direct meta-analyses (base case scenarios) comparing active treatments to placebo and did not note clinically appreciable variability between the effect estimates for percent change in LDL-C for individual studies across three distinct populations. There was however [redacted]

In general, the ERG considers the company's assumptions and recommendations regarding the handling of effect modifiers and the steps taken in sensitivity analysis to be relevant and adequate in light of the available evidence and its limitations. Specifically, the ERG agrees with assumptions and recommendations with respect to considering background ezetimibe/statin use, uniformity of active treatment doses/regimens, degree of similarity sufficient for establishing a placebo node as an anchor, and selecting time points of assessment outcome.

The ERG does not agree with company assumption that for the base-case analyses differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) would not impact the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations (even after excluding outlier studies ODYSSEY HIGH FH[39] and ODYSSEY OUTCOMES).[14] The ERG considers the company's assumptions and recommendations regarding the handling of effect modifiers and the steps taken in sensitivity analysis to be relevant and adequate in light of the available evidence and its limitations.

The ERG observes that most studies in NMA included either participants with history of CV (ASCVD) event, those with risk equivalent (ASCVD-RE or PPER), or both groups. In addition, studies used inconsistent definitions and criteria for categorizing CV risk. These inconsistencies coupled with poor reporting (e.g., for many studies proportion of people intolerant to statins, ASCVD, CHD, PPER were not reported) is a limitation of evidence which complicates any type of comparison for CV risk. Inevitably, the studies may have been imbalanced in the distribution of CV risk (both observed and unobserved factors) across the trials in NMA. Overall, the ERG team believes that this imbalance was likely to compromise the transitivity assumption to certain degree.

The company assessed the consistency assumption by comparing the agreement between the effect estimates of direct and indirect comparisons of the same two treatments (ezetimibe versus placebo) for 2 closed loops in the ASCVD and/or PPER population on MTD of statins network (Company's clarification response, question A20, page 32). For both loops, there was an agreement between the direct and indirect evidence, suggesting no evidence of inconsistency. However, the company did not provide consistency assessments for the remaining pair-wise comparisons in the two loops (placebo vs. evolocumab, evolocumab vs. ezetimibe, placebo vs. alirocumab, and alirocumab vs. ezetimibe). This information would allow the ERG to have a more comprehensive assessment and opinion on the consistency assumption in this NMA. Overall, the ERG believes that the evidence of agreement between the direct and indirect estimates from closed loops provided by the company gives some assurance that the transitivity assumption was not gravely violated and that the effect modifiers were not distributed systematically differentially across the network comparisons.

Due to limitations in evidence, [redacted] To maximise the available comparator evidence, [redacted]. This ensured that up-titration of alirocumab, which occurred at week 12, was complete prior to outcome assessment.

This was a conservative approach with respect to the results of the comparator studies, which, like the ORION trials, [redacted].

The ERG understands that the company justifiably was unable to conduct a meta-regression due to small number of studies per network and inconsistent definitions of CV risk across the studies. Meta-regression should not be considered when there are fewer than ten studies contributing to a single pair-wise comparison.[60] The use of meta-regression would help to explore bias due to non-uniform distribution of CV risk (and other effect modifiers) across the network of studies.

Although separate NMA models in three subgroups of participants were constructed (ASCVD/PPER on MTD statins, ASCVD/PPER intolerant to statins, and HeFH on MTD of statins), no NMA was feasible for the subgroup of HeFH participants intolerant to statins, since none of the comparator studies for this group reported the outcome(s) of interest (Document B, Figures 27-29). The ERG notes that the company did not specify what studies in HeFH participants intolerant to statins did not report the outcomes of interest.

The ERG expects a higher degree of uncertainty in the NMA's indirect effect estimates for the inclisiran vs. evolocumab and inclisiran vs. ezetimibe in ASCVD and/or PPER statin intolerant population (Document B, Figure 28, page 115). Firstly, this network consists of relatively low number of studies and secondly, indirect comparisons between inclisiran vs. evolocumab (or ezetimibe) are in great degree of separation from the nodes that are connected with direct evidence and are informed by at least one connection through indirect evidence.

The company reported some but not all indirect effect estimates of the NMA. For example, the ERG could not find the estimates for the comparison of evolocumab vs. alirocumab.
The ERG understands that the number of treatment comparators is not high, but still it would be more informative if the company presented surface under the cumulative ranking area (SUCRA) curves for the percent change in LDL-C and rankings for each type of treatment for the probability of being the best (the most efficacious).
The ERG notes that the company did not provide any information if effects of small-studies or publication bias (e.g., a comparison-adjusted funnel plot) was considered. Although this might be infeasible if the number of studies was below 10 as in this NMA.

2.6 *Adverse events*

The safety population was used for the primary safety analysis of inclisiran in the three key ORION trials as part of the company's submission. The safety population was defined as "all patients who received at least one dose of study drug".

In ORION-9, this accounted for everyone in the placebo group and 241/242 patients in the inclisiran group. In ORION-10, the safety population accounted for 778/780 patients in the placebo group and all patients in the inclisiran group. In ORION-11, this accounted for 804/807 patients in the placebo arm and 811 patients in the inclisiran group. As stated in the ORION-11 CSR, one subject in the placebo arm received an inclisiran dose and thus was included in the inclisiran arm of the safety population.

An AE was defined as "An AE was defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product", in the CSR.

The proportion of patients who received all four doses of their allocated drug and mean subject-days of exposure are shown in Table 21. No patients discontinued due to TEAEs in ORION-9, 13 patients (8 in inclisiran; 5 in placebo) discontinued in ORION-10, and 4 patients (all from inclisiran arm) discontinued in ORION-11.

There was no treatment switching reported in the CS.

The safety profile of inclisiran was not affected by geographic region, baseline demographic characteristics, baseline disease characteristic or comorbidities in subgroup analyses conducted for all ORION trials.

Table 21: Extent of exposure to treatment in the ORION trials

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2.6.1 Overview of adverse events

2.6.1.1 ORION-9

Table 48 of the CS (section B.2.10.1.1; page 144) provides a summary of the adverse events in ORION-9 experienced by the safety population. AEs were experienced by 76.8% of patients in the inclisiran arm and 71.7% in the placebo arm of ORION-9. A higher proportion of patients in the placebo arm experienced a TESAE compared to the inclisiran arm (13.8% vs 7.5%). There were no treatment-related TESAE or discontinuations due to TEAE in either group, and one death in each group.

2.6.1.2 ORION-10

Table 51 of the CS (section B.2.10.2.1; page 146) provides a summary of the adverse events in ORION-10 experienced by the safety population. AEs were experienced by 73.5% of patients in the inclisiran arm and 74.8% in the placebo arm of ORION-10. A slightly higher proportion of patients in the placebo arm experienced a TESAE compared to the inclisiran arm (26.3% vs 22.4%). One patient in the placebo arm (0.1%) and two patients in the inclisiran arm (0.3%) experienced treatment-related TESAEs, and there were 11 deaths in the placebo arm (1.4%) compared to 12 deaths in the inclisiran arm (1.5%).

2.6.1.3 ORION-11

Table 54 of the CS (section B.2.10.3.1; page 149) provides a summary of the adverse events in ORION-11 experienced by the safety population. AEs were experienced by 81.5% of patients in the inclisiran arm and 82.7% in the placebo arm of ORION-11. The proportion of patients in the placebo arm who experienced a TESAE compared to the inclisiran arm (22.5% vs 22.3%, respectively) were similar. No patient in the placebo arm but four patients in the inclisiran arm (0.5%) experienced treatment-related TESAEs, and there were 15 deaths in the placebo arm (1.9%) compared to 14 deaths in the inclisiran arm (1.7%).

2.6.2 Serious adverse events (SAEs)

SAEs were defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, resulted in a significant change in the subject, required hospitalisation, was a congenital anomaly, or a medically significant event which required medical judgement.

10.6% of subjects in ORION-9 experienced at least one SAE, and the prevalence of SAEs were higher in the placebo arm compared to the inclisiran arm (13.8% vs 7.5%, respectively). Table 50 of the CS presented the most common SAEs in ORION-9.

Almost one quarter of subjects in ORION-10 experienced at least one SAE, and the prevalence of SAEs were higher in the placebo arm compared to the inclisiran arm (26.3% vs 22.4%, respectively). Table 52 of the CS presented the most common SAEs in ORION-10.

Slightly over one-fifth (22.4%) of subjects in ORION-11 experienced at least one SAE, and the prevalence of SAEs were similar between groups (22.5% in placebo vs 22.3% in inclisiran). Table 56 of the CS presented the most common SAEs in ORION-10.

The most common SAEs were related to cardiovascular events.

2.6.3 Common adverse events

The incidence and risk ratio of the most common TEAEs (≥5% in any treatment group) are presented in Table 49 (section B.2.10.1.2; page 144) for ORION-9, Table 53 (section B.2.10.2.4; page 148) for ORION-10, and Table 55 (section B.2.10.3.2; page 149) for ORION-11.

In ORION-9, there were zero injection site reactions in the placebo arm and 22 (9.1%; 37 events) patients with injection site reactions in the inclisiran arm. There no were statistically significant differences in the risk ratio for the remaining common AEs.

In ORION-10 only bronchitis was a borderline statistically higher risk in the inclisiran arm (46 patients; 5.9%; 54 events), compared to the placebo arm (30 patients; 3.9%; 38 events). This resulted in a risk ratio of 1.5 (95% CI: 1.0 to 2.4).

In ORION-11, there no were statistically significant differences in the risk ratio for the most common AEs.

2.7 *Additional work on clinical effectiveness undertaken by the ERG*

No additional work was undertake by the ERG.

2.8 *Conclusions of the clinical effectiveness section*

- The population in the CS decision problem divided the population into

a) secondary prevention population (adults with Atherosclerotic Cardiovascular Disease [ASCVD]) and

b) *primary prevention populations* (primary prevention population with elevated risk [PPER] and

c) *adults with a history of heterozygous familial hypercholesterolaemia [HeFH]).* The population is narrower than the marketing authorisation as only hypercholesterolaemia patients with a serum LDL-C of ≥2.6mmol/L are considered.[12] The company have sought to align the population in the submission with that

- The ERG has some concerns that without genetic testing some HeFH cases will be missed.
- Use of the [redacted] threshold is supported by existing trial data and are supported by the [redacted] and does not address the full scope of the decision problem.
- The exclusion of bempedoic acid as a comparator appropriate given the ongoing NICE appraisal. Ezetimibe would have been an appropriate active comparator.
- The ERG agree with the exclusion of apheresis as an outcome due to rare use in clinical practice.
- Overall**,** the ERG considers the chance of systematic error in the clinical effectiveness SLR to be low**.** Overall, the ERG has no concerns with the quality of the studies included.
- Evidence for the clinical effectiveness of inclisiran comes from three RCTs: ORION-9, ORION-10 and ORION-11, were Phase III, randomised, double-blind, placebo-controlled trials. The objectives of the ORION trials were to assess the efficacy, safety, and adverse-event profile of inclisiran over a period of 18 months in patients at high risk for

cardiovascular disease in whom LDL cholesterol levels were elevated despite receiving statin therapy at the maximum tolerated dose with or without additional lipid-lowering therapy.

- Inclusion criteria in the ORION trials were mostly identical except for disease history and serum LDL levels to reflect the indications in each trial as specified below:

ORION-9: inclusion criteria was subjects with history of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented history of untreated LDL-C of >4.9 mmol/l (190 mg/dl), and a family history of FH, elevated cholesterol, or early heart disease, and serum LDL ≥2.6 mmol/l,

ORION-10: inclusion criteria was subjects with history of ASCVD, and serum LDL ≥1.8 mmol/l,

ORION-11: inclusion criteria was subjects with history of ASCVD or ASCVD-RE (T2D, FH, and including patients whose 10-year risk of a CV event assessed by Framingham Risk Score or equivalent has a target LDL-C of <2.6 mmol/l, and serum LDL ≥1.8 mmol/l for ASCVD patients or ≥2.6 mmol/l for ASCVD risk-equivalent patients at screening.

- ORION-9 and ORION-11 were international and multi-centred, both having been undertaken in 8 countries across Europe, South Africa and North America. ORION-9 recruited patients across 47 centres and ORION-11 across 72 centres. ORION-10 recruited study participants across 146 centres in the United States of America only. Only ORION-11 recruited patients from the UK; 462 patients from 23 sites.
- Overall, treatment with inclisiran resulted in statistically significant decreases in LDL-C levels (change in LDL-C and the time-adjusted percentage change) across all three ORION trials for both co-primary endpoints.

ORION-9 : The percentage change in LDL-C from baseline to Day 510 in the inclisiran group was a 39.7% decrease compared to an increase of 8.2% in the placebo group, resulting in a statistically significant between group difference of -47.9% (95% CI: -53.5 to -42.3%; p<0.001).

ORION-10: The percentage change in LDL-C from baseline to Day 510 in the inclisiran group was a 51.3% decrease compared to an increase of 1.0% in the placebo group, resulting in a statistically significant between group difference of -52.3% (95% CI: -55.7 to -48.8%; p<0.001).

ORION-11: The percentage change in LDL-C from baseline to Day 510 in the inclisiran group was a 45.8% decrease compared to an increase of 4.0% in the placebo group, resulting in a statistically significant between group difference of -49.9% (95% CI: -53.1 to -46.6%; p<0.001).

- The company provided an indirect treatment comparison of thirty-nine eligible RCTs evaluating the efficacy and safety of inclisiran as well as specific treatment comparators (i.e., alirocumab, evolocumab, ezetimibe, and placebo) along with outcomes of interest.
- Separate NMA models in three subgroups of participants were feasible (ASCVD/PPER on MTD statins, ASCVD/PPER intolerant to statins, and HeFH on MTD of statins), no NMA was feasible for the subgroup of HeFH participants intolerant to statins, since none of the comparator studies for this group reported the outcome(s) of interest.
- The ERG notes that the treatment nodes were connected correctly in the three NMA plots. The ERG considers the company's overall approach for assessing the feasibility of NMA to be appropriate, as it conforms the existing NMA recommendations.
- ORION-10 and ORION-11 were pooled in the NMA based on the similarity between baseline characteristics, LDL-C levels and overall methodology. Subgroup analysis between the trials to explore if pre-defined factors were differentially distributed across the two pooled studies would be informative.
- High statistical heterogeneity was observed in the NMA comparing alirocumab and placebo in the HeFH population. ODYSSEY HIGH FH had the highest mean baseline LDL-C compared to the other studies in this network which may cause it to be an outlier and may explain the relatively limited efficacy of alirocumab in this population.
- The ERG does not agree with company assumption that for the base-case analyses differences in CV risk and severity of patients within each population strata of interest would not impact the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations. The ERG considers the company's assumptions and recommendations regarding the handling of effect modifiers and the steps taken in sensitivity analysis to be relevant and adequate in light of the available evidence and its limitations.
- Studies used inconsistent definitions and criteria for categorizing CV risk. These inconsistencies coupled with poor reporting (e.g., for many studies proportion of people intolerant to statins, ASCVD, CHD, PPER were not reported) is a limitation of the evidence which complicates assessment of the impact of CV risk on treatment efficacy, and may have compromised the assumption of transitivity.

- **ASCVD and PPER on Maximally Tolerated Dose (MTD) statins group**

- Heterogeneity in ASCVD/PPER MTD of statins populations

  [redacted] The company clarified that a [redacted] I^2 does not necessarily imply important between-study differences. It would be more informative if the company conducted a subgroup analysis of the trials to explore if certain pre-defined factors (e.g., age, proportion of people intolerant to statins, ASCVD status, mean baseline LDL-C) were differentially distributed across the studies pooled in direct meta-analyses. [redacted]

  [redacted]ASCVD and ASCVD PPER intolerant to statins group

- [redacted]

  [redacted]HeFH on MTD of statins group

High statistical heterogeneity was detected in a direct meta-analysis of RCTs.

[redacted]

3 COST EFFECTIVENESS

This section focuses on the economic evidence and analyses submitted by Novartis, and additional information received from the company in response to the ERG's clarification questions. The ERG critically appraised the evidence and examined the company's electronic model that was submitted in Microsoft Excel.

We compare the economic analysis to the NICE reference case,[61] and provide a critique using frameworks on best practice for reporting economic evaluation and economic modelling in order to assess the overall reporting quality and validity of these analyses. In the subsequent chapter, where possible, we have addressed our concerns in the form of additional analyses.

The submission received by the ERG included:

- A systematic review of the economic evidence for the treatment of people with ASCVD, HeFH or PPER.
- Clinical and cost-effectiveness evidence, and methods used to undertake the economic analysis. The company's economic analysis results (base-case, sensitivity, scenario, and subgroup analysis results).
- Electronic version of the Markov model built in Microsoft Excel.

3.1 *Summary of the company's economic analysis*

Novartis undertook an economic to analysis the cost-effectiveness of inclisiran compared to other lipid lowering therapies for treating people with hypercholesterolaemia. A Markov model based heavily on that submitted in TA393[2], was used to depict the natural history of people with hypercholesterolaemia in terms of cardiovascular (CV) events. Three populations were modelled; ASCVD, PPER and primary HeFH, with mean baseline characteristics varied according to each population as reflected in the ORION clinical trials. Post-event health states for revascularisation, UA, MI, IS and states for CV and non-CV death were assigned. Movement between health states was dependent upon time since event and severity of event. Milder non-fatal events occurring within a given post non-fatal (NF)-CV event health state were captured as one-off costs and quality-adjusted life year (QALY) losses.

Baseline risks for each CV event were taken from an analysis of the CPRD database (CS Document B, Appendix L), which provides 1-year event probabilities for each population, and rates were adjusted to reflect the baseline age and LDL-C of the specific population entering the model.

Treatment effects were assumed to reduce the risk of CV events by lowering LDL-C levels. This was modelled as percent change from baseline LDL-C using values taken from the company NMA, for inclisiran and all comparators, with changes in LDL-C converted into change in CV event rates using data from CTT meta-analyses[62].

HRQoL data was taken from the Ara and Brazier[63] study used in TA393[2] and cost of CV events based on CG181[64], uplifted to current cost year, and NHS reference costs. Cost of SoC reflected the same proportion of patients across high, medium and low intensity statins and ezetimibe that was observed in the ORION clinical studies.

The analysis was undertaken from the NHS and PSS perspective. The clinical outcomes reported were life-years gained and quality-adjusted life years (QALYs) gained. Cost outcomes included drug acquisition and administration costs and health state costs. The results were presented as an incremental cost effectiveness ratio (ICER), expressed as cost per QALY gained. Both costs and benefits were discounted at 3.5% per annum.

The company undertook several sensitivity and scenario analyses, and probabilistic sensitivity analysis (PSA) to assess the robustness of the base-case results to changes made in model inputs/assumptions. Results for subgroup populations with ASCVD with HeFH, statin intolerance and serum LDL-C levels ≥4.0 mmol/L and ≥5.0 mmol/L were also presented.

In the ASCVD population, inclisiran is [redacted] Results from the one-way sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except for [redacted] which had the greatest impact.

The probabilistic sensitivity analysis suggested that at a £10,000 willingness-to-pay (WTP) threshold for a QALY, inclisiran had a [redacted] probability of being cost-effective when compared to SoC, and [redacted] probability at a £20,000 WTP threshold.

In the PPER population, [redacted]

In the primary prevention HeFH population,
[redacted]

PSA results for all 3 populations indicated a good level of certainty in the ICERs presented and little variation with scenario analyses initially presented by the company.

3.2 *ERG comment on company's review of cost-effectiveness evidence*

The CS (Appendices G, H and I) provides detailed reports of three systematic reviews, aimed at identifying; a) cost-effectiveness studies; b) HRQoL studies; c) cost and resource use. The purpose of conducting these SLRs was for developing an economic model that could be used to assess the cost-effectiveness of inclisiran versus other lipid lowering therapies for people with hypercholesterolaemia.

Cost-effectiveness studies SR

Searches in four bibliographic databases were undertaken on 31st July 2020. Searches combined broad terms for the population (encompassing CVD, atherosclerosis, hypercholesterolaemia) with relevant treatments (Inclisiran, evolocumab, alirocumab, ezetimibe, statins), along with a wide variety of cost-effectiveness terms in the large medical databases (MEDLINE and Embase). Some publication types were excluded in the MEDLINE and Embase searches (for example, editorials, letters, erratum and reviews), as were conference abstracts published before 2017. Searches were further limited to humans, English language and records published from 2010 onwards. The search used the Ovid limit 'humans', which is not best practice because it limits to only those articles indexed with humans as a thesaurus term and will miss the newest articles. MEDLINE and Embase searches were undertaken simultaneously via embase.com, an approach that makes searches more complicated to construct and less transparent. The ERG is unable to test embase.com, but note that searches for natural language terms/synonyms in the title and abstract fields were included and and although it appears only Embase indexing terms were used, some mapping to MeSH terms for MEDLINE

will have occurred. Five conferences are listed as being reviewed, but these were not hand-searched. This is justified because ‘citations from the searches included abstracts from all the above mentioned congresses’, but the ERG notes that “searches of Embase will not necessarily find all the trials records in a conference issue”.[65, 66] The CS states that some hand-searching of reviews, grey literature and HTAs was undertaken, but specific sources, search terms and results are not reported for these.

HRQoL SR

The original search was undertaken on 14th December 2017, with an update in May 2020. Searches in Embase and MEDLINE combined terms for outcomes and health state utilities, but also study design (e.g. RCT, observational, systematic reviews). Additionally, there were various limits applied to the original 2017 search; editorials, erratum, letters, notes, conference abstracts prior to 2015, humans, English language, publications prior to 1990. The 2020 update search was appropriately restricted by date using the sd (since date) field. The searches were conducted in the two databases simultaneously via embase.com and used the Ovid limit ‘humans’, which are not ideal as mentioned in 3.2. Terms and syntax in each line appear to be accurate and combined appropriately, but line four in the original search is reported as retrieving far fewer results than line five, despite having the same terms plus several more. Additionally, the reference lists of selected systematic reviews were checked for the original search (CS Appendix H, Section H2 and Figure 1).

Cost and resource use SR

Three separate bibliographic database searches were undertaken in February/March 2020 for the cost and resource use systematic review. These searches sought: 1. familial hypercholesterolaemia and atherosclerotic cardiovascular disease burden articles; 2. broader systematic reviews of the burden of atherosclerotic cardiovascular disease or risk-equivalent conditions published in the last five years; and 3. treatment guidelines for familial hypercholesterolaemia and atherosclerotic cardiovascular disease. For the first two questions, Embase, MEDLINE and Cochrane Library were searched independently via Ovid, while the TRIP database was searched for the third. A reasonable variety of terms for the populations, economic and humanistic burden were included in the first two searches and various language, date, publication type, age and animals/humans limits were mostly applied appropriately, an exception being the animals limits in tables 2, 3, 5 and 6 of CS Appendix I, which would have

removed any records indexed as both humans and animals. The TRIP database search may not be comprehensive enough, but there is limited reporting for this search. The ERG re-ran the search on 16th December 2020 in the search option that appears to have been used (https://www.tripdatabase.com/#pico), then filtered the results by 'guidelines' under 'Evidence type', but found that no UK guidelines were retrieved. Removing the term 'guidelines' from the PICO 'Outcomes' box retrieved five UK guidelines.

3.2.1 Results of systematic reviews

The aim of the cost-effectiveness study SR was *"to identify previous economic evaluations in cardiovascular risk reduction in ASCVD, HeFH and ASCVD high-risk equivalent patients"* (CS Document B, Appendix H). The scope is clear and a sensitive search conducted. 63 studies and 15 HTAs were included in the cost-effectiveness SR (CS Appendix G, Table 8 (UK), Table 10 (non-UK) and Table 11 (HTAs)). The included UK studies are summarised in CS Document B Table 57.

63 studies were included, of which 19 studies evaluated PCSK9 inhibitors and the remaining 44 studies assessed interventions other than PCSK9 inhibitors such as statins or ezetimibe (CS Doc B Section B.3.1). The company reported that ultimately, *"No economic evaluations of inclisiran in hypercholesterolaemia or mixed dyslipidaemia were identified in the cost-effectiveness SLR."* (CS Doc B, Section B.3.2)

However, the company also note a single economic evaluation was identified after the cost-effectiveness SLR was conducted[67], although this was disregarded on the grounds it was conducted from Australian healthcare payer perspective and did not cover all populations addressed within this submission.

The ERG reviewed the recent study by Kam[67] (summarised in Appendix 1) which uses a simplistic Markov-cohort model with 3 health states, and models only risk of non-fatal MI in patients with ASCVD, to evaluate cost-effectiveness of inclisiran in the Australian health care system. The ERG agree this study contributed little information to directly inform this economic evaluation.

The aim of the HRQoL SR was *"to identify recent studies reporting health state utilities (HSUVs) for patients presenting with any major adverse cardiovascular (CV) events (MACE), including,*

non-fatal myocardial infarction (MI), non-fatal stoke, unstable angina (UA) and revascularisation…" (CS Document B, Appendix H). 214 studies were included in the SR, one of which, a study by Ara & Brazier[63], was used in the cost-effectiveness analysis.

A health-state cost and resource use SR was undertaken by the company although the aim of this is not clear. 28 studies were included in the results, however the company state that despite the search, "sources used in previous appraisals have been retained for consistency" (CS Document B, pg. 194). It therefore does not appear that the SR was used at all in the company submission.

3.2.2 Interpretation of the review

The ERG is satisfied with the company's SLR searches and that all key studies used for inputs have been reported. However, reliance on the model submitted and sources used for inputs in the previous TA393[68] appraisal for alirocumab, was noted.

The ERG believes that using existing published evidence (e.g. in peer-reviewed studies and previous NICE appraisals) serves as useful input to the submitted economic model. However, the ERG would have welcomed further critique of the identified studies regarding the resource use and costs, and health state utility studies.

3.3 *Summary and critique of the company's submitted economic evaluation by the ERG*

In this section, the ERG appraises the company's economic analysis against the NICE reference case[20] for technology assessment. The ERG provide a summary of the company's illustrative model structure, as well as the clinical (treatment effect on CV event risks, mortality) and economic evidence (drug acquisition and administration costs, post-CV event health state management costs) used to parameterised the economic model. Along with the summary, the ERG provides a critique of methods and inputs used in the economic analysis in the following sections.

3.3.1 NICE reference case checklist

The ERG appraised the company's economic evaluation against the NICE reference case[20]. Our findings are reported in Table 22.

Table 22: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes - company reports 'incremental' results with comparison to the base-case, ICERs versus baseline and fully incremental cost-effectiveness estimates
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes - Life time horizon
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes – Results reported in terms of quality adjusted life-years
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes - Age-adjusted baseline disutilities based on Health Survey for England
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, benefit is estimated based on EQ-5D responses of appropriate UK populations, scored using UK time trade off-tariff
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Element of health technology assessment	Reference case	ERG comment on company's submission
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.3.2 Model structure

The company submitted a Markov cohort model with 1-year cycles. Half cycle correction is applied, as is an annual discount rate of 3.5% to both costs and health outcomes. An NHS and personal social services perspective is adopted and modelled over a lifetime time horizon. Although a de novo model for this submission, the structure is based primarily on the model presented by the company in the NICE TA393 submission.[2]

The key difference is the partitioning of the ACS health state into MI and UA health states within this submission. This enables different effects to be attributed to each health state facilitating more accurate representation of costs and outcomes.

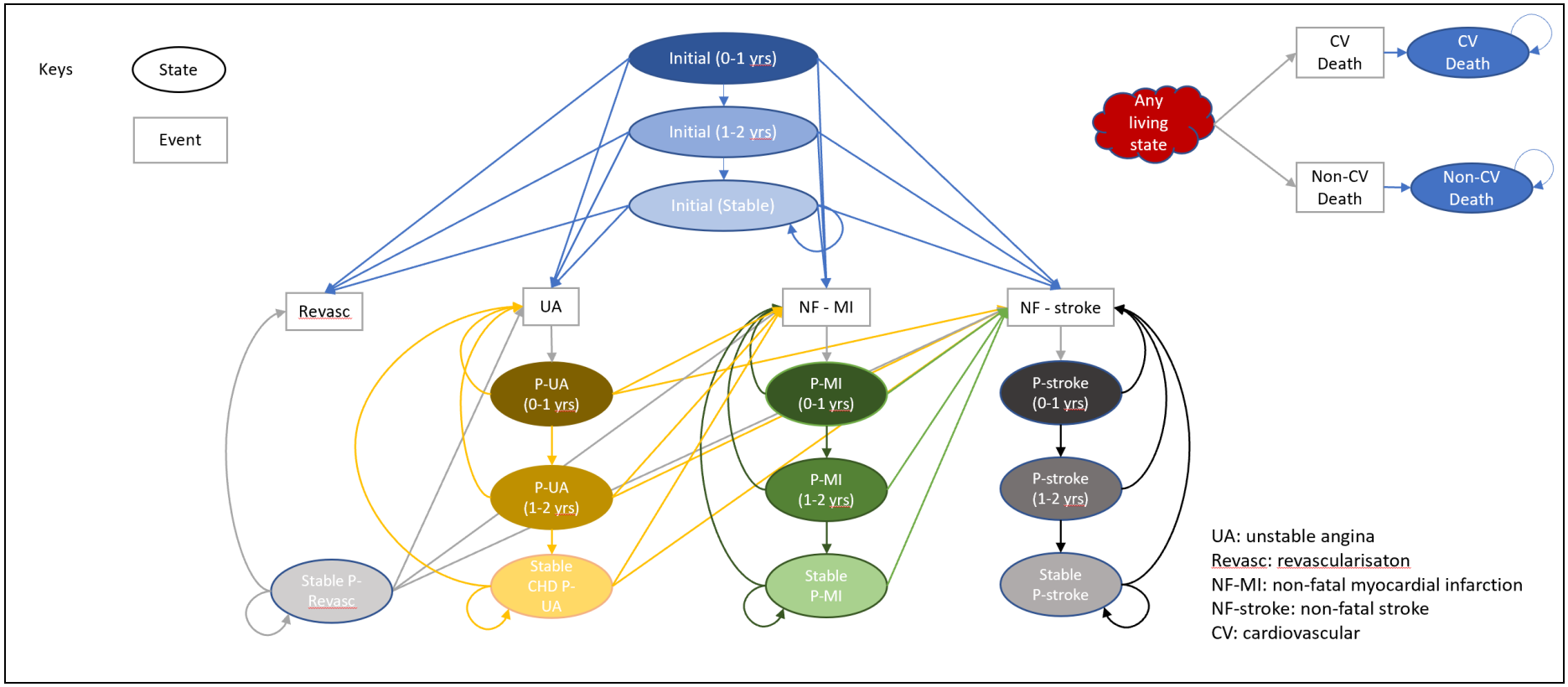

Figure 1. Illustrative Markov model structure

The model comprises 15 mutually exclusive discrete health states (see Figure 1) with annual transitions from one state to another based on predicted risks of CV events (fatal and non-fatal) and risk of death from non-CV causes:

- Initial (0–1; 1–2; stable)
- Post event states for:
    - revascularisation
    - unstable angina (UA) (0–1; 1–2; 2+ years)
    - NF-MI (0–1; 1–2; 2+ years)
    - NF-stroke (0–1; 1–2; 2+ years)
    - CV death
    - non-CV death

A full description of passage through the model and transition assumptions are provided by the company (CS Document B, Section B.3.2.2, pg. 173).

The ERG note distinction between the initial states on model entry and the later division of post, non-fatal, CV event states into years 0-1, 1-2, and stable. The model was constructed this way due to increased risk of further events occurring in the first year post CV event, originally implemented in the alirocumab submission,[2] and mirrored here by the company.

Transition only occurs to a 'worse' health state to ensure logical HRQoL outcomes remain over time. It was observed in TA393[2] that patients could move from a post-event health state e.g. stroke, with lower HRQoL outcomes, to a better one e.g. if they subsequently experienced an MI, which has higher HRQoL outcomes. In lieu of transition to a milder, non-fatal event state, a one-off cost and QALY decrement associated with each specific event is applied.

The ERG finds the Markov model structure fit for purpose in modelling hypercholesterolaemia, as a long-term condition with future CV sequelae. It is suitable for use with the subgroup populations presented in this submission and incorporation of time-dependent risks was achieved using tunnel states both on entry to the model and post-event. The ERG finds the assumption that transition can only occur from a 'milder' to a 'worsened' health state plausible, and application of a one-off cost/ utility decrement when a 'milder' event is experienced is appropriate. However, it is recognised this would not capture any compounding effects on

HRQoL which may be caused due to subsequent events. This is a limitation of the multiplier approach, similarly, present in previous submissions for hypercholesterolaemia,[2] and as so comparability with this submission is preserved.

The ERG finds the model structure appropriate for this submission.

3.3.3 Population

The company considers the following populations in their economic analysis:

Secondary prevention population

- Adults with ASCVD (including HeFH) and serum LDL-C [redacted] despite maximally tolerated statins.

Primary prevention population

- Adults who are primary prevention with elevated risk (PPER) with serum LDL-C [redacted] despite maximally tolerated statins
- Adults with a history of HeFH without ASCVD and serum LDL-C [redacted] despite maximally tolerated statins (CS Document B, Pg. 157).

The company address these populations separately throughout the submission and economic evaluation due to differences in the current recommendations made for patients with non-familial and familial hypercholesterolaemia. Patient characteristics also differ between these populations, therefore consideration of these groups independently is appropriate.

The company expect marketing authorisation to be granted for use of inclisiran 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 population presented in this submission is narrower than the marketing authorisation as only hypercholesterolaemia patients with a serum LDL-C of [redacted] are considered. The

company have sought to align the population in the submission with [redacted]

The company provide justification for this approach by citing results from previous clinical trials, which observe greater absolute risk reduction in patients with baseline LDL-C [redacted] than those with lower baseline levels[14]
and from this infer that inclisiran would be expected to provide the greatest clinical benefit in this population. The company also point to this threshold having historically been considered a threshold for up-titration and add-on therapy for PCSK9 inhibitors,[18] and aligns approximately with the mean baseline LDL-C levels observed in the ORION-10 and ORION-11 trials. (CS Document B, pg. 17-18).

Whilst these arguments support the use of ≥2.6 mmol/L as a clinically effective threshold, they do not account for the complete population falling under the marketing authorisation of inclisiran. For example patients with an LDL-C <2.6mmol/L may need to reduce LDL-C further to achieve target treatment levels (for high risk <1.8 mmol/L and very high risk <1.4 mmol/L as outlined in ESC/EAS guidelines[10]) . Likewise, primary HeFH patients with LDL-C <2.6mmol/L who need to reduce to minimum achievable levels would also be missed.

In summary, the ERG finds:

Consideration of the three distinct populations appropriate within this submission.

Use of the [redacted] threshold is supported by the literature, where the aim is to establish the cost-effectiveness in this specific population.

[redacted]

3.3.3.1 Subpopulation

The three populations were further stratified by presence of HeFH, severity of hypercholesterolemia and statin intolerance or contraindication. This addressed the subgroups outlined in the NICE scope. These subgroups are summarised in Table 23.

Table 23. Subgroups included in the economic model (Table 58, CS Document B pg. 169)

Subgroup	HeFH	LDL-C	Statin intolerant
ASCVD	✓	≥3.5 mmol/L (and very high risk of CVD[†]) ≥4.0 mmol/L	✓
PPER	×	×	✓
HeFH w/o ASCVD	×	≥4.0 mmol/L ≥5.0 mmol/L	✓

Abbreviations: CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; PPER, primary prevention with elevated risk.
[†]Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).

Levels of severity of hypercholesterolemia were defined based on current NICE recommendations for alirocumab and evolocumab.[2, 15]

The ERG believes this is appropriate.

3.3.4 Baseline characteristics

Baseline characteristics are taken from the ORION-9, ORION-10 and ORION-11 clinical trial CSRs provided with the CS (see. Table 24) and have been incorporated into the model with patient characteristics varied in line with the specific population being modelled. Calculation of the mean baseline LDL-C levels to the specified minimum LDL-C for each population is then enabled, as is variation by diabetes status and treatment status at baseline.

Table 24. Baseline characteristics in each population (Table 63, CS Document B pg. 179)

Population		Age	% female	% diabetes	LDL-C	Source
Secondary prevention	ASCVD and serum LDL-C [redacted]	64.75	34%	38%	3.47	ORION-10 and -11 CSRs ASCVD patients
Primary prevention	PPER and serum LDL-C [redacted]	62.28	54%	66%	4.02	ORION-11 CSR PPER patients
Primary prevention	HeFH without ASCVD and serum LDL-C [redacted]	52.36	58%	7%	4.09	ORION-9 CSR

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PPER, primary prevention with elevated risk.

CV event history at baseline within the ASCVD group is addressed by modelling a mixed cohort of patients with previous events. Each cohort is run individually then the weighted average across sub-populations calculated. Weights are derived by hierarchical assessment of the CPRD analysis (CS Document B, Appendix L) to categorise patients (see Table 25). The methodology is described in detail in the CS Document B (p.174). It is of note, for each sub-population of the cohort modelled, baseline characteristics from the ORION-trial population are kept constant and different risks are assigned. This methodology was also used for the ASCVD population in TA393[2], although weights in that submission were elicited from the THIN database[69] and varied markedly from those obtained through CPRD (see table 28 for relative weights). The company did not address any variation in the weights of differing CV event histories in any of their exploratory analyses. Therefore, the ERG undertook a scenario analysis to assess the impact of using weights from this alternative source (see results Section 4).

Table 25. Definitions and weights for sub-populations (Adapted from table 61, CS Document B pg. 174) with population weights for ASCVD from CPRD and THIN databases

Sub-population	Definition	Weight CPRD	Weight THIN
ACS 0-1	UA or MI in the previous 12 months	9%	3.28%
ACS 1-2	UA or MI in the previous 12-24 months	1%	2.83%
Other CHD	ACS events >2 years ago or other evidence of CHD	62%	68.55%
IS	A history of IS	19%	11.05%
PAD	A history of PAD	9%	14.29%

Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; IS, ischaemic stroke; MI, myocardial infarction; PAD, peripheral artery disease; UA, unstable angina.

The ERG finds the use of baseline characteristics sourced from the ORION trials appropriate and the methodology and rationale for modelling the ASCVD population suitable for this submission. However, scenario analysis is undertaken to determine the impact of sub-population weights in the ASCVD cohort.

3.3.5 Baseline risks

3.3.5.1 CPRD analysis

Baseline CV risks were taken from an analysis of the CPRD (provided to ERG as Appendix L, CS Document B). CPRD is a longitudinal, anonymised research database derived from primary-care practices in the UK. The company selected the Aurum database within this, which contains [redacted]. This provided annual event risks for each model state, separately, for patients with and without diabetes.

[redacted]

As event risks obtained from the CPRD data were over a 12-month period, adjustment for increasing risk over time was included at 3% per year increase in non-fatal CV events and 5% per year increase in CV deaths. This adjustment, is sourced from a modelling study[70] and also applied in TA 393.[2]

The company use this calculation to adjust baseline event rates to the average age of the modelled population, taken from the ORION-9, -10 and -11 trial CSRs (see Table 26). Similarly, adjustment for prevalence of diabetes within the population is also made, using CPRD event rates obtained separately for patients with without diabetes then weighting them according to prevalence found in ORION-9, -10 and -11 trial populations. No adjustments were made for gender split between trial populations for CV-events, as the company assume CPRD data is reflective of the UK population and therefore differential gender risks are accounted for (CS Document B, Pg. 175). Adjustment for non-CV mortality by gender was made.

Table 26. Population characteristics in the CPRD analysis (Table 64, CS Document B pg.181)

Population	Age	% female	% diabetes	LDL-C
ASCVD and serum LDL-C [redacted]	68.77	45%	16%	3.47
HeFH without ASCVD and serum LDL-C [redacted]	52.62	64%	2%	4.75
PPER and serum LDL-C [redacted]	65.73	33%	15%	3.63

The ERG find the unpublished CPRD study (CS Document B, Appendix L) a well-conducted [redacted] However, the ERG note:

This study is subject to the common limitations found in this type of [redacted]

Similar sources of longitudinal data, such as THIN[69] database have been used in other appraisals for lipid lowering therapies including TA393.[2] The THIN database contains electronic medical records of 11.1 million patients from 562 GP practices across the UK, representing 6.2% of the population.[69]

Both THIN[69] and CPRD[71] data are widely used for research purposes although publication outputs from these primary care electronic databases show output from CPRD[71] more than double that from THIN[69] data, increasing particularly in recent years. [72] As was highlighted in the TA393 company submission,[73] a substantial portion of the THIN[69] cohort used to inform mean baseline LDL-C levels were not on optimised statin therapy. [redacted] (CS Document B, Appendix L).

The inherent challenges seen within the CPRD database[71] occur across other large datasets, and may be balanced by the benefits gained from large population samples. However, as large and well-validated databases, the ERG believe these remain representative sources to extract baseline CV risks for modelling purposes and research. The use of CPRD[71] over THIN[69] data may be most beneficial in terms of population size, drawing upon the electronic records of [redacted]

In section 3.3.2.2. (CS Document B, pg. 182) the company raise concerns regarding inconsistencies in outcomes from CPRD for the HeFH population and discuss these findings as the rationale for using CV event data from an alternative source for the secondary prevention HeFH sub-group. The ERG address this in detail in section 3.2.5.2. below. Given the caution expressed by the company this sub-group, it is interesting that this is not discussed in the context of the larger primary HeFH population and suggestions of alternative data sources made.

The ERG finds the use of CPRD data appropriate and assumptions and adjustments made to the data plausible in this submission.

3.3.5.2 Secondary prevention HeFH

The company reported identification of inconsistencies in CPRD data (CS Document B, Appendix L) in the of risk of events in the secondary prevention HeFH population. Multiple explanations were cited from their clinical experts suggesting explanations for errors in FH in the primary-care database. A likely cause was patients being coded as having FH in CPRD databases but no confirmation obtained by genetic testing. Also, coding errors occur where patients are inadvertently diagnosed with FH. In these instances, event rates are generated by patients who may not be true HeFH cases, leading to an underestimation of CV events (CS Document B, pg.181).

Whilst acknowledging these potential inaccuracies may result in mislabelling of FH, the ERG conversely notes that FH is often diagnosed and managed in the secondary care setting. [redacted] This would also contribute to under-informing CV event rates in the HeFH population. The ERG supports the consensus that results for the FH population from CPRD data analysis should be interpreted with caution, though question why this is only raised in the context of finding an alternative source for the analysis of the secondary HeFH subgroup population. Justification for using an alternative source of CV event data could be made on the same grounds for the primary HeFH population (section 2.10.5.1.).

The company chose to run an analysis using data from the Mohrschladt et al, 2004[1] study which provides data for CV events (fatal and non-fatal) in HeFH patients, delineated by primary or secondary-prevention populations. The main rationale for using this data to inform their base-case analysis for the secondary prevention population was that it had been used previously for the base-case for this population in the TA393[2] submission.

The company highlight the relative merits of Mohrschladt et al., 2004[1] study such that it reports rates of all CV events of interests separately e.g. MI, UA, revascularisation, stroke and that included patients have a confirmed diagnosis of HeFH. The company also acknowledge a limitation of the study being its small sample size with only 131 secondary prevention HeFH (CS Document B, pg. 182). The ERG notes the publication date for the Mohrschladt et al. study 2004 and absence of any discussion by the company regarding more recent data sources they may have considered using for this analysis. Only the questionable CPRD data analysis (CS Document B, Appendix L) was used for scenario analysis.

The ERG identified several more recent studies[74, 75] which reported CV event data in the HeFH population, published after TA393.[2] Summaries of the study characteristics, compared with those of Mohrschladt et al., 2004[1] are presented in Table 27.

Table 27. Summary of studies reporting CV event rate data in HeFH populations

Study/Characteristics	Mohrschladt 2004[1] (Secondary HeFH)	Beliard 2018 [74] (Secondary HeFH)	Galema-Boers 2018 [75] (Primary and secondary HeFH combined)
Age (Mean)	54	60	Mean not reported
Gender (% male)	64%	72%	47%
Number of participants	131	565	821 (combined)
Years of follow up	1105	5779	8538
CV rate for all events (per thousand person years) (# of events)	143/1000 (158)	90/1000 (778)	12/1000 (102)
Fatal CV event rates (per thousand person years) (# of events)	12/1000 (13)	1.4/1000 (8)	0.5/1000 (4)
Mean LDL-C (mmol/L)	7.27	8.0	7.7

Both more recent studies[74] have substantially larger cohorts and years of follow up than Mohrschladt et al., 2004,[1] whilst retaining the benefits for use in modelling of reporting individualised CV events. The Galema-Boers, 2018[75] study was most robust in its reporting of both sampling methodology and the types of statins used. All patients were on maximally tolerated doses of statins, with definition of maximally tolerated doses included, and a more even split of males to females (47:53) was observed. However, the cohort consisted mainly primary prevention HeFH patients with only 12% secondary prevention and outcomes for both groups combined.[75] Therefore, this paper serves as a good cross check to CPRD data obtained for the HeFH population but cannot be used for secondary HeFH subgroup analysis.

The Beliard, 2018[74] study has a greater proportion of males than in Mohrschladt et al., 2004,[1] (72% v 64%), lower average baseline LDL-C levels (3.7mmol/L v 7.27mmol/L) and only 48% of patients were on statin therapy compared with all patients who were put on statins within the initial 6-8 weeks of the Mohrschladt study (89% of whom remained on them). However, Beliard[74] confirmed diagnosis of HeFH using genetic testing on 75% of participants and using the full Dutch Lipid Clinic Network criteria. [76] Although the company state patients in Mohrschladt et al., 2004,[1] had a confirmed diagnosis of HeFH (CS Document B, pg. 182), no genetic testing was performed and assessment was made using on a restricted number of criteria from the Dutch Lipid Clinic Score.[76]

In the Beliard[74] study, both non-fatal CV event rates and CV death rates were lower than those in Mohrschladt (90 v 143 per 1000 patient years and 1.4 v 12 per 1000 patient years, respectively). This may be accounted for due to the difference in LDL-C levels (3.7mmol/L v 7.27mmol/L). However, the difference in LDL-C levels is notable between the two study populations, and may not be accounted for by study setting (French HeFH registry of lipid clinic patients and Dutch lipid clinic, respectively). Authors of the Beliard[74] study concluded they found a high rate of recurrent events, in comparison to other recent studies, suggesting their cohort consisted more severe HeFH population being managed in a lipid clinic. The ERG are concerned that data from Mohrschladt et al., 2004,[1]may be an overestimate of event rates in the secondary prevention HeFH population and produce a lower ICER for patients in this subgroup treated with inclisiran + SoC.

The scenario analysis conducted by the company, using the CPRD data analysis (CS Document B, Appendix L) with lower event rates, is presented in the results section and shows an increase in the ICER as would be expected. However, the ERG was unable to replicate these results due to technical errors within the model so cannot be confident in the figures presented.

The ERG would like to run a scenario analysis using event rates from Beliard, 2018,[74] given the strengths of this study, to investigate the impact on the ICER. Unfortunately, this is not possible due to the technical errors in the model.

Without further investigation, uncertainty remains around the most appropriate source of event rates and the corresponding for ICER for this subgroup.

The ERG finds use of the Morschladt et al. 2004[1] data for event risks in the secondary prevention HeFH population reasonable for comparison with previous TA393[2] submission, but note CV events may be overestimated and more current data is available. Justification of using an alternative to the CPRD as the company's base-case is supported. Further scenario analysis of the Beliard 2018 and CPRD verification is required to fully investigate results for this population.

3.3.6 Translating changes in LDL-C to changes in risk

No outcomes data for inclisiran is available currently as the main trial for assessing this, ORION-4, is due to report in 2024 (CS Document B, pg.152). Therefore, the company use the

intermediate outcome of reduced LDL-C levels, associated with a reduction in CV events, to establish the same outcome relationship in the economic model.

This approach has been used previously in the submission for alirocumab with the same rationale at point of submission.[2] Outcomes data for this comparator intervention has since become available and patient-level data used in a cost-effectiveness model.[77] This showed improved cost-effectiveness in the cohort of patients with baseline LDL-C [redacted]. However, costs were modelled from a U.S. private payer perspective so cost-effectiveness cannot be extrapolated to the UK setting.[77]

In lieu of inclisiran outcome data, CV event rates obtained from CPRD analysis (and Mohrschladt et al.[1] for secondary prevention HeFH population) were adjusted to reflect baseline event rates for baseline LDL-C levels in the ORION-9, -10 and -11 populations (as reported in the CSRs provided with the CS), thereby establishing rates of SoC for each.

A log-linear relationship, reported in previous meta-analyses[78] and used widely in hypercholesterolaemia submissions, was used by the company to translate change in LDL-C levels to change in CV event risks, in lieu of outcomes data for inclisiran.
The following equation was applied by the company, which allowed baseline event risks to be increased or decreased as required according to the difference between the ORION and CPRD population average LDL-C levels:

$$E_i = E_{0i} * \alpha_i^{L_0 - L_1},$$

where:

- L_0 *is the baseline LDL-C level in mmol/L*
- L_1 *is the new LDL-C level in mmol/L*
- E_{0i} *is the 1-year probability for experiencing event i at the baseline LDL-C level of* L_0
- E_i *is the 1-year probability for experiencing event* i *at the LDL-C level of* L_1

- α_i *is the "rate ratio" (RR) per unit change in LDL-C for event* i.

The CTT analysis[62] estimates rate ratios per 1.0mmol/L decrease in LDL-C levels in statin patients vs control patients for various levels of risks of CV events. As the company report, the CTT analysis[62] is based on 28 large-scale RCTs including a large number of patients who have been on statin therapy for over 2 years (CS Document B, pg. 185). This assists in capturing the demonstrated link between treatment duration and treatment effect, whereby reduction in RR per mmol/L is smaller in the first year of treatment.[79] The company were also able to directly obtain RRs for individual CV event outcomes relevant to the model, including CV death, MI, stroke and revascularisation, as these were directly reported in the CTT analyses. As the model considers only IS, rather than all strokes as reported in the latest CTT analysis,[62] the company use a RR for this from a previous CTT analysis.[80] Table 28 summarises the RRs applied in the model.

Table 28. Effects on major coronary events, strokes, coronary revascularisation procedures, and major vascular events per 1.0 mmol/L reduction in LDL-C at different levels of risk estimated from CTT meta-analyses[62]

Event	RR per 1.0 mmol/L reduction in LDL-C	95% CI
Revascularisation	0.75	0.72, 0.78
NF-MI	0.73	0.70, 0.76
Stroke (any)	0.81	0.77, 0.86
Vascular death	0.84	0.80, 0.88
IS	0.79	0.74, 0.85

Abbreviations: CI, confidence interval; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; NF-MI, non-fatal myocardial infarction; RR, rate ratio.

The ERG finds use of intermediate outcome data appropriate at this stage and in line with methods used in TA39. The ERG considers the use of the CTT meta-analysis[62] to model the relationship between LDL-C and CV event risks appropriate.

It is noted that outcome data is now available for alirocumab and evolocumab and inclisiran outcome data is expected as part of the ORION-4 clinical trial due to read out in 2024.

3.3.7 Interventions and comparators

Intervention

The intervention under consideration is inclisiran (284 mg) administered as a subcutaneous injection. Delivery occurs on Day 1, Day 90, and then at 6-month intervals as an adjunct to maximally tolerated statin and other lipid-lowering therapy. This is aligned with the dosing schedule used in ORION-9, -10, and -11 clinical trials (as reported in the CSRs provided with the CS).

Comparators

The comparators presented by the company are not directly aligned with those specified in the final scope published by NICE.[81] Bempedoic acid has not been included as a comparator in this analysis and ezetimibe has been included as part of SoC rather than separately as an active comparator (see Section 1.4.3. for full discussion within the decision problem).

Bempedoic acid

Bempedoic acid, either with a statin, or in a fixed dose combination with ezetimibe alone or with a statin, has not been considered as a comparator by the company. The company's justification for this omission is that bempedoic acid in both forms is subject to an ongoing NICE appraisal and therefore cannot be considered part of established clinical practice.

The ERG finds this approach is appropriate given this is the precedent set within HTA assessments. However, it is noted:

Bempedoic acid, with or without fixed dose ezetimibe (available as a combined tablet), is orally administered, whereas inclisiran is injected.

The manufacturers are also seeking marketing authorisation in the UK for treating primary hypercholesterolaemia or mixed dyslipidaemia and the proposed position in the clinical treatment pathway of bempedoic acid (+/- fixed dose ezetimibe) is the same as inclisiran.

This suggests that bempedoic acid is an extremely pertinent comparator to inclisiran and following the second committee meeting for GID-TA10534 on 5th November 2020, publication of NICE guidance is anticipated imminently. If approved, whilst not part of established clinical

practice, the availability of another treatment option in the primary care pathway with an alternative route of administration may prove significant in both prescription and uptake of inclisiran.

Ezetimibe

The company have considered standard-of-care (SoC) to be a *"population-specific mix of maximally tolerated statins (including no statins in patients who are contraindicated or intolerant to statins) and other lipid-lowering therapy, including ezetimibe"* (Pg. 177, CS). In this way, the company removed ezetimibe as a comparator, instead including it as part of SoC, thereby incorporating its efficacy as that of background therapy in all arms.

The rationale used by the company to justify this approach includes:

1. Use of ezetimibe in clinical practice has remained infrequent (4.1% in ASCVD, 1.5% in PPER, 5.4% in HeFH; (CS Document B, Appendix L).

The study provided in Appendix L is a [redacted] The figures reported by the company reflect the findings using this methodology on a large and representative UK dataset. However, it is of note that [redacted].

The ERG noted use of ezetimibe at baseline in subgroups of the ORION clinical trials populations as illustrated in Table 29. The proportion of patients taking ezetimibe delineated by

trial were 51% in ORION -9 (patients with HeFH and elevated LDL-C), 11% in ORION -10 (patients with ASCVD and elevated LDL-C) and 9% in ORION -11 (patients with ASCVD or PPER and elevated LDL-C). (Obtained from PLD sheet, company model submission).

Table 29. Composition of SoC by patient population (Table 76, CS Document B pg. 193)

Population	*No LLT*	*High intensity statin*	*Moderate intensity statin*	*Low intensity statin*	*Ezetimibe*	*Other LLT*	*Source*
ASCVD and serum LDL-C [redacted]	*8%*	*66%*	*18%*	*1%*	*10%*	*12%*	*Pooled efficacy dataset (ORION 10 and 11)*
ASCVD and serum LDL-C ≥4.0 mmol/L	*21%*	*52%*	*13%*	*1%*	*13%*	*13%*	
ASCVD and serum LDL-C ≥3.5 mmol/L	*17%*	*55%*	*15%*	*0%*	*12%*	*12%*	
People with statin intolerance	*51%*	*0%*	*0%*	*0%*	*24%*	*25%*	
HeFH and serum LDL-C [redacted]	*7%*	*72%*	*15%*	*2%*	*51%*	*4%*	*ORION-9*
ASCVD and serum LDL-C [redacted]	*4%*	*81%*	*12%*	*1%*	*53%*	*3%*	
ASCVD and serum LDL-C ≥3.5 mmol/L	*7%*	*76%*	*13%*	*1%*	*51%*	*1%*	
Without ASCVD and serum LDL-C [redacted]	*8%*	*69%*	*15%*	*2%*	*51%*	*4%*	
Without ASCVD and serum LDL-C ≥5.0 mmol/L	*24%*	*55%*	*10%*	*3%*	*34%*	*5%*	

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering therapy.

Whilst it might be expected that a clinical trial population treatment would more closely resemble therapy guidelines at baseline, due to trial inclusion criteria, there may be case that usage of ezetimibe in these populations lies between that of trial data and estimates from real-world sources. This is most probable in the primary heterozygous-familial hypercholesteriolaemia

population due to limitations in reporting in real-world data sources (see section 3.2.5.1 for discussion).

2. Feedback from clinical experts suggests that whilst patients do achieve some reduction in their LDL-C level with the addition of ezetimibe to a statin, it is counter-productive, as this reduction in LDL-C prevents patients from being eligible for more advanced therapies (PCSK9i) that are likely to offer a greater reduction.

The ERG sought clinical expert advice regarding use of ezetimibe in clinical practice. Feedback suggested if LDL-C levels are not on target following generic statin therapy (atorvastatin or simvastatin) then clinical decision, inclusive of patient's preference, was made to either switch to rosuvastatin (not yet generic) or add ezetimibe. There was no suggestion of any reason, apart from side effects or patient choice, for patients not trial ezetimibe.

The ERG do note that guidelines for eligibility to PCSK9i therapy is dependent on risk category/mmol/L LDL-C levels (TA393, TA394)[2, 15] but emphasise there is no barrier to treatment for patients on ezetimibe, either with or without statin current treatment, purely due to its prescription.

3. Based on clinician input from a NICE submission Advisory Board Meeting, July 2020 where "experts noted it is possible that guidelines for treatments may change with the treatment landscape".

The ERG notes that at the NICE submission Advisory Board Meeting the company expressed their concern that if ezetimibe was included in the NICE submission as an active comparator (instead of as the standard of care) it would reduce the number of patients eligible for inclisiran. They expressed a strong stance that ezetimibe should be the standard of care.

The advisory board were clear in their directions, and the consensus from both clinical and health economics perspectives was that NICE guidelines treat ezetimibe as an active comparator. Ezetimibe should not be treated as the standard of care in the company's submission:

- NICE is looking for the value of new treatments versus current therapies
- The board agreed on the importance of comparing inclisiran with all available treatment options for the NICE submission.

This is in parallel with the final scope produced by NICE for appraisal of bempedoic acid, where ezetimibe is listed as an active comparator.[82]

NICE guidance on the use of ezetimibe in UK clinical practice is given in TA385, published in 2016 and due for review in February 2019.[83] Upon enquiry, the ERG were advised by NICE that "following internal discussions, we do not believe that any potential review will affect ID1647 appraisal" (personal communication – Celia Mayers, Administrator – Technology Appraisals & HST, email 10/12/2020). The ERG remains unclear as to whether a review of this topic is underway or planned.

Guidance given in TA385[83] is to be used in conjunction with NICE clinical guidelines on Familial hypercholesterolaemia: identification and management (CG71).[13] Detailed within the guidance the following recommendations:

- *Offer a high-intensity statin with the **lowest acquisition cost** as the initial treatment for all adults with FH and aim for at least a 50% reduction in LDL C concentration from the baseline measurement. [2017]*
- *When prescribing ezetimibe co-administered with a statin, ezetimibe should be prescribed based on the lowest acquisition cost. [2016]*

An important theme, emboldened within the published guidance, was achieving optimal treatment at lowest cost. This was in the context that an increasing number of statins were becoming available in generic form, atorvastatin being one of these. Up-titration of therapy to achieve at least a 50% reduction in LDL-C levels using generic statin options rather than those still on-patent would achieve lowest acquisition cost. Similarly, as annual acquisition costs of ezetimibe at the time of review were £343.20 (2015 cost year), generic statin up-titration, if possible, prior to prescription of ezetimibe would also ensure lower acquisition costs.

Significantly, ezetimibe's patent expired in October, 2017 [84] leading to significant price reduction, and costs now in-line with other lipid-lowering therapies (see Table 30).

The Committee on TA385[85] did not consider any anticipated price fall associated with patent expiry at the time of review, as there were 2 years remaining on-patent and *"a specified price had to be available and guaranteed across the NHS"* (pg 2 of the committee papers[85]).

However, the ERG believe revised cost-effectiveness estimates of ezetimibe due to this price reduction are now appropriate, and pertinent within this appraisal. The full marketing authorisation for both inclisiran and ezetimibe includes primary hypercholesterolaemia (heterozygous-familial and non-familial) patients, not just those with LDL-C levels [redacted] It is highly likely that ezetimibe, even with lower overall efficacy in LDL-C reduction than inclisiran, could provide a highly cost-effective option for an important proportion of the population in this appraisal, to achieve target LDL-C levels.

Table 30. Unit costs and resource use for SoC (Table 75, CS Document B pg 193)

Drug	***Representative drug***	***mg/unit***	***Units/ pack***	***Cost/ pack***	***Dose***	***Units/ year***	***Cost/ year***
High intensity statin	*Atorvastatin*	*40*	*28.00*	*£1.42*	*40 mg daily*	*365.25*	*£18.52*
Moderate intensity statin	*Atorvastatin*	*20*	*28.00*	*£1.15*	*20 mg daily*	*365.25*	*£15.00*
Low intensity statin	*Simvastatin*	*10*	*28.00*	*£0.89*	*10 mg daily*	*365.25*	*£11.61*
Ezetimibe	*Ezetimibe*	*10*	*28.00*	*£1.95*	*10 mg daily*	*365.25*	*£25.44*

The ERG conclude ezetimibe should be included as an active comparator to Inclisiran, as per the final scope,[81] and not included as part of the SoC as the company have disputed.

The ERG pursued the reason for the company's chosen approach during the clarification process. Whilst the company reiterated their position, they helpfully provided results of cost-effectiveness analyses, including ezetimibe+SoC as an active comparator, for the ASCVD and PPER populations. These results are presented in detail in the results section.

In summary, the ERG finds:

Omission of bempedoic acid as a comparator appropriate at this point in time.

Inclusion of ezetimibe as SoC inappropriate. Ezetimibe should be considered as an active comparator in this submission.

3.3.8 Perspective, time horizon and discounting

The NHS and personal social services perspective was taken over a life-time horizon with discount rate of 3.5% applied for both costs and outcomes (QALYs). These approaches are implemented appropriately within the model and are in line with recommendations for the NICE reference case.[61]

3.3.9 Treatment effectiveness and extrapolation

Treatment efficacy is taken from the NMA, detailed in the company submission (CS Document B, Section B.2.9.), with comprehensive analysis and critique given by the ERG in sections 2.5 and 2.6 of this report.
The outcome selected for efficacy was percentage change in LDL-C at 24 weeks in all populations. Assumptions made by the company are:

- Treatment efficacy constant across all baseline LDL-C categories
- Patients in the SoC arm do not experience any change in LDL-C categories (feedback received from medical experts at an advisory board run by Novartis)
- All drugs to be used in addition to maximally tolerated statins

Efficacy was estimated separately for patients with ASCVD or PPER and patients with HeFH, and a scenario analysis for statin intolerant patients was also provided for the ASCVD and PPER populations.

The ERG finds the assumptions regarding treatment efficacy plausible.

The ERG sought to evaluate several NMAs reported in table 12 appendix D as a sensory check in addition to the most recently published NMA, an abstract by Toth et al. (2020)[24] in an effort to obtain results from NMAs using most recent data.

As with the nature of an abstract the ERG was unable to judge the methodology and validity of this NMA and do not know which studies they included, excluded, or why. Therefore, there may have been systematic differences in the study selection between this and company NMA. It was noted that the NMA abstract included studies with participants taking moderate plus high intensity statins, whereas the company NMA excluded low and moderate statin intake studies,

leaving only MTD or intolerant to statins. Moreover, the abstract NMA included bempedoic acid as a comparator, whereas it was justifiably excluded from the company NMA.

However, a comparison of the primary outcome results (LDL-C % reduction from baseline to week 12) between the active treatments vs. placebo in the two NMAs (Table 31), shows they are in good agreement. Given this rationale, the company NMA remains the most trustworthy source and the recent abstract does not add anything new.

Table 31. Comparison of efficacy outputs from NMAs

Intervention	% LDL-C reduction from baseline to W 12 versus placebo	
	Toth et al.[23] abstract	Company NMA
Evolocumab (140mg Q2W)	-64.73 (-67.42, -62.03)	[redacted]
Alirocumab (150mg Q2W)	-62.71 (-67.56, -57.87)	[redacted]
Inclisiran (300mg)	-50.17 (-55.00, -45.35)	[redacted]
Ezetimibe (10 mg QD)	-24.64 (-27.68, -21.60)	[redacted]

The ERG concludes that the NMA conducted by the company is the most trustworthy source of efficacy data for inclisiran and its comparators and is appropriate for use in this submission. The assumptions regarding treatment efficacy plausible.

3.3.10 Discontinuation of inclisiran and PCSK9 inhibitors and statins

One hundred percent treatment adherence was assumed in the company's base-case over the model lifetime horizon. This assumption is in line with the economic analysis from TA393. In scenario analyses, discontinuation rates for inclisiran and PCSK9is were obtained from the clinical trials, while treatment discontinuation rates for alirocumab and evolocumab were obtained from the ODDYSEY Outcomes and FOURIER trials, respectively. Annual discontinuation rates ranged from 1.7% to 5.7%. A second scenario assumed that a 5% annual discontinuation rate across all treatments. With respect to discontinuation of statins, the company undertook a separate analysis that considers the impact of patients discontinuing statins. Rates for the discontinuation of statins were obtained from the ORION trials. It was assumed that people who discontinued statin treatment reverted to their baseline LDL-C and thus, have higher risks of cardiovascular events.

The ERG considers these scenario analyses to be appropriate.

3.3.11 Non-CV mortality

Rates of non-CV mortality were taken from lifetables for England and Wales[86] which have then been adjusted to remove the proportion of deaths due to CV causes using cause-specific mortality data.[87]

The ERG finds this appropriate.

3.3.12 Health related quality of life

3.3.12.1 Health utility values

Utility values representing health related quality of life (HRQoL) are calculated using study results from Ara & Brazier[63] which provide estimates of age- and gender-adjusted utilities for people with no history of CV disease:

*EQ-5D Utility = 0.9454933 + 0.0256466*male - 0.0002213*age - 0.0000294*age^2*

Baseline utility values for each starting cohort were then derived by applying multipliers to these values. Utility multipliers are shown in Table 32. These were taken from TA393[2] as the approach used in this submission based upon that used in the alirocumab appraisal.

Table 32. Baseline utility multipliers for each cohort (Table 23, CS Document B pg. 190)

Starting cohort	*Utility multiplier*
HeFH primary prevention	*1*
HeFH secondary prevention	*0.924*
ACS 0-1	*0.765*
ACS 1-2	*0.924*
Other CHD	*0.924*
Stroke	*0.822*
PAD	*0.924*
PPER	*1*

Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; PAD, peripheral arterial disease; PPER, primary prevention with elevated risk.

Additional utility multipliers were applied when a patient experiences an event. These are presented in Table 33, also sourced by the company from TA393. [2] This one-off QALY loss is applied to patients experiencing an acute event whilst being in a more severe health state within

the model and have been calculated as “the difference in utilities between Year 1 post-event and the stable post-stroke utility, regardless of the baseline health state.” (CS Document B pg. 191)

Table 33. Post-event utility multipliers (Table 24, CS Document B pg. 191)

Event	*Event multiplier, 1st year*	*Event multiplier, 2nd year*	*Event multiplier, beyond Year 2*
Revascularisation	*–*	*–*	*1.00*
UA	*0.77*	*0.96*	*0.96*
NF-MI	*0.77*	*0.91*	*0.91*
NF-Stroke	*0.78*	*0.82*	*0.82*

Abbreviations: MI, myocardial infarction; NF, non-fatal; UA, unstable angina.

The ERG note HRQoL data was not available from the ORION clinical trials at point of company submission. A SLR was conducted to identify relevant studies from the published literature which in theory was to inform the decision problem. The company retrieved 214 relevant studies and provided a complete description of the search strategy and tabulated summaries of the studies identified (See Appendix H, CS). However, no rationale for the choice of study used, or discussion of its merits is provided in this submission. The company simply state ‘this approach was validated by clinical and health economics experts at an Advisory board’.

Selection of the Ara & Brazier study[63] was justified by the company in the TA393 submission, as based on the SLR they conducted *“it was the most complete and coherent source of utility values for all the health states in the model”* (pg. 225, TA393 CS document).[73]

The ERG is satisfied that utility values, and method in which they are applied, are appropriate within this submission. The ERG is confident that the methods used to elicit these values in the TA393[2] appraisal were rigorous, and that no comprehensive, more recent data is available to replace these estimates. Similarly, the ERG supports the use of this approach to mirror that in previous submissions, the importance of which was highlighted at the advisory board meeting.

3.3.12.1.1 Adverse events

Across the ORION studies, inclisiran was associated with a similar nature and frequency of adverse events as placebo (ERG report section 2.6.1). However, more inclisiran-treated patients reported treatment-emergent adverse events (TEAEs) at the injection site than

placebo-treated patients (8.2% vs 1.8% recorded TEAEs at the injection site, respectively). Across the studies; 0.2% inclisiran-treated vs 0.0% placebo arm patients, discontinued due to these TEAEs [Appendix C, CS]. These reactions were reported as localised, predominantly mild or occasionally moderate, transient (i.e. resolving prior to the next dose), and resolved without sequelae (Section B.3.4.4, CS).

For the purposes of this submission, the company concluded injection site reactions were relevant TEAEs for the inclisiran and PCSK9 inhibitors and state that the "incidence of relevant TEAEs was included for inclisiran and comparators, and a disutility and/or cost was applied". (Section B.3.4.4, CS). The company excluded AEs associated with SoC on the basis that it is common to all treatment arms in the model in baseline comparison, so any expected influence on cost-effectiveness would be minimal.

The ERG finds this approach justified due to the nature of the TEAEs. However, on investigation the ERG was unable to locate the disutility values attributed to these TEAEs within the model and no values were reported within the submission document. Both 'control' and 'clinical data' sheets displayed a figure of 0.00 in the relevant cells.

Later in the submission document the company states "Adverse events have not been incorporated into the model" (Section B.5.3.5, CS)

The ERG finds reporting of the methodology used to address adverse events inconsistent within the company submission. Ultimately, adverse events have not been included. However, given the nature and distribution of these events (primarily injection site reactions) and minimal subsequent management required, the ERG believes the addition of disutility/cost would not have an impact on the ICER.

3.3.13 Resources and costs

3.3.13.1 Intervention and comparators

List prices for evolocumab and alirocumab, sourced as cost per dose from the British National Formulary (BNF)[88] are applied for these comparators, as the discounted prices are not publicly available (see Table 34).

Table 34. Unit costs and resource use for PCSK9 inhibitors (Table 74, CS Document B pg.191)

Drug	*Strength (mg)*	*Units/ pack*	*Cost/pack (£)*	*Dose*	*Source*
Inclisiran	*284*	*1*	[redacted]	*284 mg at Day 0, Day 90 and then every 6 months thereafter*	*Novartis*
Evolocumab	*140*	*2*	*340.20*	*140 mg every 2 weeks*	*BNF[88]*
Alirocumab	*75 or 150*	*1*	*168.00*	*75–150 mg every 2 weeks*	*BNF[88]*

Abbreviation: BNF, British National Formulary.

The company included per-cycle costs for SoC, but as the company maintain that Ezetimibe is part of SoC, the cost of Ezetimibe was incorporated with the cost of statins when determining a value for each statin intensity.

A representative therapy was selected for each statin intensity by choosing the most commonly prescribed statin at each intensity in the ORION-11 clinical trial. Unit costs and resource use for each therapy level were taken from the BNF[88] with the proportion of patients taking high, moderate or low intensity statins based on those being used at baseline in the relevant subgroup of the ORION clinical trial programme where available (see section B.3.3.1, CS, for details of SoC composition by patient population). Drug tariff prices were used, as per the NICE reference case, as statins and ezetimibe are prescribed mainly in primary care setting. (See Table 35)

Table 35. Unit costs and resource use for SoC (Table 75, CS Document B pg.193)

Drug	**Representative drug**	**mg/ unit**	**Units/ pack**	**Cost/ pack**	**Dose**	**Units/ year**	**Cost/ year**
High intensity statin	Atorvastatin	40	28.00	£1.42	40 mg daily	365.25	£18.52
Moderate intensity statin	Atorvastatin	20	28.00	£1.15	20 mg daily	365.25	£15.00
Low intensity	Simvastatin	10	28.00	£0.89	10 mg daily	365.25	£11.61

statin							
Ezetimibe	Ezetimibe	10	28.00	£1.95	10 mg daily	365.25	£25.44

Abbreviations: SoC, standard-of-care.

The company assumed the cost of administration for inclisiran to be 10 minutes of nurse time, taken from the Unit Costs of Health and Social Care 2019. [89] Administration costs for alirocumab, evolocumab and SoC were assumed to be zero, upon consideration that all components are either self-injected or oral therapies. Despite these drugs being self-administered, the company do raise the point that the majority of patients receiving these treatments remain in secondary care which clinical input suggests is in order to receive the patient-access scheme (PAS) price which is not available in primary care. By proxy, these patients would receive additional monitoring in secondary care. Additionally, the cost of one-off training for self-injection of alirocumab and evolocumab has not been included (Section B.3.5.1, CS Document B pg. 194).

The ERG finds the reasoning, methodology and sources for costing appropriate. However, the ERG does not support the company's inclusion of ezetimibe as part of SoC (discussed in detail in section 3.2.4.2 of this report).

3.3.13.2 Health-state unit costs and resource use

A systematic review of costs and resource use was undertaken by the company, results detailed in Appendix I of the CS. However, there was no discussion of the relative merits and limitations of included studies, and the company state, "sources used in previous appraisals have been retained for consistency." (CS Document B, pg. 194)

Acute costs for CV events were retrieved from NHS reference costs, whilst post-event costs were taken from CG181 and TA393 and inflated from 2013/14 to 2018/19 prices using the HCHS pay and prices index.[89] The cost of CV death was also based on the cost per death in the TA393 submission to NICE.

Costs in the stable states are applied beyond Year 3. This was recommended by the ERG in TA393, on the basis that patients following cardiovascular events (such as stroke) may require ongoing social care and medical attention.[73] See Table 36 for CV event costs applied in this submission.

Table 36. Cost of CV events split by year (Table 78, CS Document B pg. 195)

Event	Acute (£)	Year 1 (£)	Year 2 (£)	Stable (£)
MI	2,366.95	851.26	851.26	851.26
UA	1,661.63	415.91	415.91	415.91
Stroke	4,750.72	167.44	167.44	167.44
Revascularisation	6,780.01	N/A	N/A	0.00
CV Death	1,268.25	N/A	N/A	N/A

The ERG was unable to deduce exactly how costs had been calculated from CG181 without more refined referencing provided by the company. Additionally, during clarification it was questioned why only post-event costs were taken from this source and inflated to present day values. CV event costs were also available from CG181/TA393[2, 64] (Table 40) but instead the company chose to use current NHS reference costs, despite reasoning that use of figures from previous NICE submissions was to retain consistency. This generated substantially decreased cost estimates for acute CV events in this submission compared with CG181/TA393[2, 64] (MI - £2,366.95 vs £3,337; UA - £1,661.63 vs £3,313; and revascularisation - £6,780.01 vs £3,802). The only exception was acute cost of stroke, which increased from £4,092 £4,750.72 from CG181/TA393[64] to current appraisal, respectively. This appears more in line with increases expected due to inflation across cost years, illustrated by inflated costs of post-event and CV death costs from 2014 to 2020 prices. (See Table 37 and Table 38 for comparison).

Table 37. Cost of CV events split by year in alirocumab appraisal (Table 69, pg. 233 TA393 CS)

Event	*Acute (£)*	*Year 1 (£)*	*Year 2 (£)*
MI	*3,337*	*788*	*788*
UA	*3,313*	*385*	*385*
Stroke	*4,092*	*155*	*155*
Revascularisation	*3,802*	*N/A*	*N/A*
CV Death	*1,174*	*N/A*	*N/A*

ACS, acute coronary syndrome; CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; N/A, not available; NF, non-fatal; UA, unstable angina

The company provided comprehensive detail in response to clarification questions, including sources contributing to estimates derived in CG181, [2, 64] as far as were reported (see Q.A14,

Clarification Responses)

Rationale underpinning the approach taken with acute event costs was outlined. Acute event costs are assumed to be the cost of the hospitalisation only. All other costs are captured in the post-event costs and it is assumed that event costs in CG181 are primarily derived from NHS reference costs. It was considered more appropriate to update acute event costs using the latest version of the NHS reference costs (2018/2019) than to inflate reported costs from CG181[64] (which are from 2014), as this will better reflect any changes in the provision of care. The company provided the event costs as they would have been if they had updated all costs from TA393. }[2] Scenario analyses using these cost estimates were also provided for the three populations considered in this submission (See section 4.2 for results).

Table 38. Event costs updated from TA393 (Table 25, Clarification Response, pg 36)

Event	Acute (£)	Year 1 (£)	Year 2 (£)	Stable (£)
MI	3,604.91	851.26	851.26	851.26
UA	3,578.98	415.91	415.91	415.91
Stroke	4,420.53	167.44	167.44	167.44
Revascularisation	4,107.24	N/A	N/A	0.00
CV death	1,268.25	N/A	N/A	N/A

Abbreviations: CV, cardiovascular; MI, myocardial infarction; UA, unstable angina.

The ERG is satisfied by the responses provided during clarification and find the rationale for costing acceptable. The ERG notes that feedback from the ERG in TA393 was incorporated, and post-event costs were applied over the full time horizon to avoid under-estimation of long-term costs associated with CV events. The notable differences between acute CV event costs in CG181/TA393 and this submission are likely explained by changes in treatment/management of hospitalised patients over time. However, scenario analyses using inflated figures for all costs in TA393 were welcome from the company, and show little impact on ICERs.

3.3.14 Summary of company base-case inputs into the economic model

A summary of the company base case is provided in Table 39.

Table 39. Summary of variables applied in the economic model

Variables	Source	ERG summary assessment	Reference to section in this report
Baseline characteristics (Age, % male, % diabetes)	ORION clinical trial program	**The ERG finds the use of baseline characteristics sourced from the ORION trials appropriate and the methodology and rationale for modelling the ASCVD population suitable for this submission. However, scenario analysis is undertaken to determine the impact of sub-population weights in the ASCVD cohort.**	Section 3.3.4
Baseline LDL-C	ORION clinical trial program	**The ERG finds the use of baseline LDL-C levels sourced from the ORION trials appropriate**	Section 3.3.4
Baseline CV risks	From CPRD	**The ERG finds the use of CPRD data appropriate and assumptions and adjustments made to the data plausible in this submission.**	Section 3.3.5.1
Rate ratios for CV events per mmol/L reduction in LDL-C	CTT meta-analysis	Varied using 95% CIs assuming a normal distribution	Section 3.3.6
Discount rate (costs and outcomes)	3.5%	Not varied	Section 3.3.8
Treatment efficacy	From the NMA	Varied in PSA using the CODA	Section 3.3.9
Distribution of SoC	ORION clinical trial program	Not varied	Section 3.3.13.1
Cost of SoC	BNF (Drug tariff)	Not varied	Section 3.3.13.1
Cost of CV events	NHS reference costs & CG181	Varied +/- 15%	Section 3.3.13.2

Abbreviations: BNF, British National Formulary; CI, confidence interval; CODA, Convergence Diagnostics and Output Analysis; CPRD, Clinical Practice Research Datalink; CTT, Cholesterol Treatment Trialists; CV, cardiovascular; LDL-C, low density lipoprotein cholesterol; NHS, National Health Service; NMA, network meta-analysis; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; PSA, probabilistic sensitivity analysis; SoC, standard-of-care.

3.3.15 Overview of model assumptions with the ERG's comments

The company made several simplifying assumptions to have a working model (see Table 40).

Table 40. Company's model assumptions with the ERG's comments

Assumption	Justification	ERG's comments
For all treatments, LDL-C reductions occur immediately upon treatment initiation.	This simplifying assumption is based on observations from the ORION clinical trial programme that inclisiran was associated with significant reductions in LDL-C at first observation post-baseline (Day 14). In order to test the impact of this assumption a scenario where the impact of inclisiran is assumed to occur at Day 90 is also tested.	The ERG considers these feasible assumptions.
When patients discontinue therapy their LDL-C returns to baseline in the following cycle.	This simplifying assumption has been made to simplify model calculations. The treatment effect for inclisiran is durable and when patients stop receiving treatment LDL-C returns to baseline levels at a rate of 2–3% per month. Thus this assumption is expected to be conservative for inclisiran. Other therapies are dosed more frequently than inclisiran and LDL-C levels are expected to return to baseline at a faster rate. This is consistent with the assumptions applied in TA393.	At clarification stage in response to the ERG's query, the company clarified that while it is anticipated that in clinical practice patients discontinuing other therapies would return to baseline levels of LDL-C at faster rates compared to those discontinuing inclisiran. The company viewed this a conservative assumption. The ERG considers this a feasible assumption.
Baseline data from the ORION clinical trials is representative of the UK ASCVD and HeFH populations	Table 63 and 64 (CS Doc B) present the baseline characteristics for the modelled populations from the ORION clinical trial data and CPRD data respectively. There is some variation in the proportion of patients with diabetes, however other estimates (THIN data used for TA393) have fallen in between these values. The data from the ORION clinical trials has the advantage of also being assessed in a population that	The ERG notes variation between baseline characteristics from ORION clinical trials and UK electronic database analyses. The company's justification for using ORION trial data is compelling. The ERG considers it a feasible modelling assumption that ORION trial baseline characteristics are representative of the UK ASCVD and HeFH populations.

Assumption	Justification	ERG's comments
	are on maximally tolerated statins, which is not the case for the CPRD analysis, and by using PLD in the model we are able to retain any correlation between characteristics when the population is changed.	
Rate ratio for CV events from the CTT meta-analysis are applicable to all years across the time horizon	While it is acknowledged that rate ratios may be smaller in Year 1 and larger in subsequent years, scenario analyses have been conducted to test this	Our understanding of this assumption is that the rate ratio for CV events are constant over time, indicating that the treatment efficacy does not change throughout the model time horizon. However, given the lack of evidence to support that treatment efficacy is maintained, the company could have provided an analysis to show the impact of a waning of the treatment effect on the cost-effectiveness results.
CPRD data is representative of event risks in the UK population	CPRD collects patient data from GP practices across the UK and encompasses 50 million patients, including 16 million currently registered patients.	The ERG considers the CPRD database suitable for the event risks in all populations except the secondary prevention HeFH population.
The relative reduction in LDL-C seen with inclisiran is constant across subgroups within the ASCVD and HeFH populations.	Data from the ORION clinical trials show minimal variation in treatment effect across subgroups.	This assumption is consistent with what was reported in the clinical trials for these populations.
ASCVD, atherosclerotic cardiovascular disease; CPRD, Clinical Practice Research Datalink; CV, cardiovasucular; CVD, cardiovascular disease; ERG, evidence review group; GP, general practitioner; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; PLD, patient-level data		

4 COST EFFECTIVENESS RESULTS

4.1 *Company's cost effectiveness results*

In this section, we present the company's deterministic results for the ASCVD, PPER, and HeFH populations.

4.1.1 Atherosclerotic cardiovascular disease

The company's base-case results showed that inclisiran + SoC when compared to SoC alone was approximately [redacted] more costly than SoC alone and expected to yield [redacted] more QALYs, which equated to an ICER of approximately [redacted] per QALY.

[redacted] These results indicate that the ICER for the comparison between [redacted]

Table 41: Deterministic base-case results in the ASCVD population

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ASCVD, atherosclerotic cardiovascular disease; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

4.1.2 Primary prevention with elevated risk

In the PPER population,

[redacted] Table 42[redacted].

Table 42. Deterministic results in the PPER population

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					

PPER, primary prevention with elevated risk; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

4.1.3 Heterozygous familial hypercholesterolaemia population

In the HeFH population [redacted] Table 43[redacted].

Table 43. Deterministic base-case results in the primary prevention HeFH

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

4.2 *Company's sensitivity analyses*

4.2.1 Probabilistic sensitivity analysis results

Results of the probabilistic sensitivity analysis are presented in Table 44 to Table 46 for the ASCVD, PPER and HeFH populations, respectively. In PSA, parameters are assigned a distribution to reflect the amount and pattern of its variation, and the cost-effectiveness results are calculated by simultaneously selecting random values from each distribution. Results for the PSA simulations for each population were plotted on cost-effectiveness planes (Figure 2, Figure 4, Figure 6), then cost-effectiveness acceptability curves (Figure 3, Figure 5, Figure 7) were generated, showing the probability that an intervention is optimal at a range of willingness-to-pay thresholds.

4.2.2 Atherosclerotic cardiovascular disease

The PSA results (Table 44) are in line with the deterministic results as shown in Table 41. Figure 2 shows that there was little uncertainty around the total costs and total QALYs for across all treatment strategies.

[redacted]

(Figure 3).

Table 44. Probabilistic sensitivity analysis results for the ASCVD population

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ASCVD, atherosclerotic cardiovascular disease; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

[redacted]

4.2.3 Primary prevention with elevated risk

PSA results (Table 45) were in line with the deterministic results (Table 42) for the primary prevention with elevated risk population. Figure 4 and Figure 5 show the PSA results plotted on a cost-effectiveness plane and CEAC, respectively. The scatterplot shows that there was some uncertainty around total QALYs and less so for the total costs. At a willingness-to-pay threshold of £20,000 per QALY,

Table 45. Probabilistic sensitivity analysis results for the PPER population

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
				-		

ICER, incremental cost-effectiveness ratio; PPER, primary prevention with elevated risk; QALY, quality adjusted life year; SoC, standard of care

4.2.4 Primary prevention heterozygous familial hypercholesterolaemia

Similarly, the PSA results for the primary prevention HeFH population are in line with the deterministic results. Figure 6 and Figure 7 shows the results of the PSA plotted on a cost-effectiveness plane and CEAC, respectively. Results on the scatterplot show that there is some uncertainty around the total QALYs. At a willingness-to-pay threshold of £30,000 per QALY, [redacted]

Table 46. Probabilistic sensitivity analysis results for the primary prevention HeFH population

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
[redacted]						
[redacted]						
[redacted]						
[redacted]						

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

[redacted]

In general, the company has varied key model input parameters by using the appropriate distributions. However, the ERG has noted that there was little uncertainty around the total costs and total QALYs, this may be a result of the narrow 95%CIs for the baseline and event utility multipliers. In the company submission document B, the company stated that in the PSA, 10,000 simulations were recorded for the ASCVD population. However, the number of simulations in the excel model provided were not in line with what the company reported. At clarification, it was unclear on the methods used to address the mixed cohort of patients when undertaking the PSA. The company provided some detail:

'Results for the mixed cohort are obtained by running the model for each cohort individually and weighted average results calculated at the end (see Table 61 of the company submission for the mixed cohort composition used in the base case). Similarly for the PSA, this was run once for each model cohort, and weighted average results were constructed.

The procedure used in PSA is:

1. *Set the population to model population 1 (Primary prevention HeFH)*
2. *Run the PSA and copy costs and QALYs for each comparator from each simulation*
3. *Repeat for populations 2 to 8 (Secondary prevention HeFH to PPER)*
4. *Calculate the weighted average costs and QALYs for each arm for each simulation, using the weights provided in Table 61 of the company submission (weighting over populations 3 to 7)*
5. *Calculate the average costs and QALYs for each arm across the simulations and use this to calculate the incremental results*
6. *Generate the cost-effectiveness plane and CEACs.'*

The ERG considers this approach reasonable. However, this approach does not include any uncertainty in the weights for sub-populations. Additionally, for step 5 it is unclear if the same number of iterations have been used before calculating the average.

4.2.5 Deterministic sensitivity analysis

Figure 8 to Figure 10 show the results of the deterministic sensitivity analysis for the ASCVD, PPER and HeFH populations, respectively. Parameters were varied either by their 95%CI or by assuming ±15% range where no confidence intervals were available. In Figure 8 and Figure 9, these results showed that the model was sensitive [redacted]. However, in the HeFH population (Figure 10), the company stated that,

[redacted]

(Company submission Document B, pg. 209).

4.3 *Company's scenario analyses*

The company undertook several scenario analyses across the populations of interest (see Table 47). In general, the base-case ICERs were robust to changes made to key model input parameters. The company found that in the scenario with differential discontinuation rates for inclisiran and PCSK9is

Table 47. Scenario analyses undertaken by the company

No.	Scenario analyses
1.	Equal efficacy for inclisiran and PCSK9is
2.	Efficacy for inclisiran taken from the clinical trials Adjusting rate ratios for CV events according to Collins et al
3.	Assuming patients discontinue all treatments at the same rate
4.	Including discontinuation of statin therapy
5.	Assuming inclisiran has no impact on LDL-C until day 90
6.	Inclusion of ezetimibe + SoC as a comparator for the ASCVD and PPER populations
7.	Using updated event costs from TA393[2] in the ASCVD population
8.	Using updated event costs from TA393[2] in the PPER population
9.	Using updated event costs from TA393[2] in the primary prevention HeFH population
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density	

lipoprotein cholesterol PPER, primary prevention with elevated risk; SoC, standard of care

In response to the ERG's clarification question A.14, the company undertook an analysis that included treatment with ezetimibe + SoC as a comparator for the ASCVD population and PPER populations. Results for the ASCVD population and the PPER populations is reported in Table 48**.** and Table 49, respectively. In Table 48, [redacted]. The comparison between [redacted]

Table 48. Cost-effectiveness results for the ASCVD population including ezetimibe as an active comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ASCVD, atherosclerotic cardiovascular disease, ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; SoC, standard of care

Table 49 reports the results of including ezetimibe + SoC treatment strategy as a comparator in the PPER population. The results show that [redacted]

Table 49. Cost-effectiveness results for the PPER population including ezetimibe as an active comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]					
[redacted]					
[redacted]					

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; PPER, primary prevention with elevated risk; QALY, quality adjusted life years; SoC, standard of care					

In the ASCVD population, the ERG noted that the ICER for [redacted] Additionally, the ERG noted the [redacted] In the PPER population, the ERG noted that the ICER for [redacted] Additionally, there was a [redacted] The ERG was unable to validate these results, as we were not supplied with the updated model with efficacy information for ezetimibe.

In response to the ERG's clarification question B.1.2, the company provided updated event costs updated from TA393,[2] then scenario analyses results for the ASCVD (Table 50), PPER (Table 51) and primary prevention HeFH populations (Table 52).

Table 50.Cost-effectiveness results for the ASCVD population, using the updated event costs from TA393[68]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 51. Cost-effectiveness results for the PPER population, using the updated event costs from TA393[68]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52. Cost-effectiveness results for the primary prevention HeFH population, using the updated event costs from TA393[68]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.4 *Company's subgroup analyses*

The company undertook several subgroup analyses. Description of these analyses along with an approximation of the ICERs for the comparison between inclisiran + SoC compared to SoC are reported in Table 53.

Table 53. Subgroup analyses results

Subgroup analysis	Description	ICER (£/QALY) for inclisiran + SoC versus SoC only
Patients with ASCVD and HeFH	This analysis considered people with a history of ASCVD and HeFH. The rates of cardiovascular events were obtained from Morschladt et al, and efficacy from the HeFH base-case analysis.	[redacted]
	The rates of cardiovascular events were derived from the CPRD analysis.	[redacted]
Severity of hypercholesterolaemia	ASCVD and serum LDL-C ≥ 4.0 mmol/L	[redacted]
	People with a high risk of CVD (defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed) and serum LDL-C ≥ 3.5mmol/L	[redacted]
	Statin intolerant patients with ASCVD	[redacted]
Primary prevention patients with elevated risk	PPER who are intolerant to statins	[redacted]
Primary prevention HeFH	Patients with HeFH without ASCVD and serum LDL-C ≥ 3.0mmol/L	[redacted]

	Patients with HeFH without ASCVD and serum LDL-C ≥ 4.0mmol/L	[redacted]
	Patients with HeFH without ASCVD and serum LDL-C ≥ 5.0mmol/L	[redacted]
	Patients with HeFH without ASCVD who are intolerant to statins	[redacted]
ASCVD, atherosclerotic cardiovascular disease; CPRD, Clinical Practice Research Datalink; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care		

4.5 *Model validation and face validity check*

The company declared that validity of the model was assessed by an external company, not involved in its development, using standard procedural checks. These included logic and consistency checks for each cell, logical model outputs and comparison of outputs to those in similar previous economic analyses (CS Document B, pg. 230).

The ERG also performed these checks and noted:

- Some cells displayed negative values in the engine worksheets.
- Cell C38 in the 'Key Results' worksheet returns a 'REF!' value in the updated model.
- Tables under PSA results in the 'Incremental results' worksheet do not update when PSAs are run.
- The cost-effectiveness plane in the 'Simulations' worksheet shows the Total costs and Total QALYs in reverse order.
- PSA results from the updated model (with ezetimibe + Soc), simulations return the same total costs and QALYs for two of the comparators.

The ERG suggest it is very unlikely these errors would have any meaningful impact on the deterministic model outputs, although navigability of the model was poor for the user.

The ERG was able to replicate deterministic base-case results for the ASCVD, PPER and primary prevention HeFH populations. Results for PSA runs were displayed across various sheets and linkage between cells/sheets were unclear. Technical assessment of the model was required with the ERG manually calculating PSA results to check (results provided in Appendix 2). This did suggest caution should be taken with the validity of PSA results.

Whilst the model is based upon the model used for TA393[2], the company acknowledge that results are not directly comparable due to a number of major differences between the analyses, including baseline event rates and the RRs used to adjust them dependent upon LDL-C levels. The company also found a large proportion of the reported outcomes in TA393[2] marked CIC therefore unavailable for comparison (CS, Document B, pg. 230). The ERG believe this is reasonable.

The ERG identified negative values during cell checks but found these likely insufficient to affect model validity. Greater concern was caused by identification of technical inaccuracies during the running of PSAs.

5 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

5.1 *Exploratory and sensitivity analyses undertaken by the ERG*

The ERG has provided a summary and critique of the company's economic model (see Section 3.3). Based on our critique, the ERG identified few changes required to company's base-case. The company provided comprehensive scenario analyses within their submission, and during clarifications, allowing the ERG to explore of several pertinent inputs.

In addition, the ERG undertook an additional scenario analysis for the ASCVD population and exploratory analysis for the secondary HeFH subgroup, providing our justification with cross-referencing to the relevant section of this report where concerns are discussed.

5.2 *Impact on the ICER of additional clinical and economic analyses undertaken by the ERG*

5.2.1 Scenario analysis using alternative weights for ASCVD mixed population

The ERG performed an additional scenario analysis using THIN database weights for ASCVD mixed cohort (Table 54).

[redacted]

Table 54. Scenario analysis results in the ASCVD population using THIN weights for mixed cohort

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs incremental (£/QALY)
[redacted]						
[redacted]						
[redacted]						
[redacted]						

ASCVD, atherosclerotic cardiovascular disease; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

5.2.2 Scenario analysis with ezetimibe as an active comparator

The ERG intended to conduct additional analyses with ezetimibe as an active comparator, rather than included as part of SoC, but this functionality was not available in the original model. During the clarification process the company provided the ERG with results of analyses for the ASCVD and PPER cohorts and submitted the updated model for critique. The company did not provide results for the primary HeFH population advising they were unable to obtain efficacy rates for ezetimibe from the NMA for this population. Results provided by the company are presented in section 4.3 of this report and ERG validated results replicated below (Table 55 and Table 56).

Table 55. Cost-effectiveness results for the ASCVD population including ezetimibe as an active comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ASCVD, atherosclerotic cardiovascular disease, ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; SoC, standard of care

Table 56. Cost-effectiveness results for the PPER population including ezetimibe as an active comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ICER, incremental cost-effectiveness ratio; PPER, primary prevention with elevated risk; QALY, quality adjusted life years; SoC, standard of care

[redacted]

5.2.3 Exploratory analysis for CV event rates in the secondary prevention HeFH population

In the company subgroup analysis for the secondary prevention HeFH (ASCVD and HeFH) population data for CV event rates was taken from Mohrschladt et al.[1] and varied in scenario analysis by using CPRD data (CS Document B, Appendix L). The results reported by the company are presented in tables Table 57 and Table 58, showing an ICER for inclisiran + SoC of [redacted] with Mohrschladt[1] and [redacted] with CPRD event rates, respectively.

Table 57. Results for patients with ASCVD and HeFH, with event probabilities from Morschladt et al.1 (Table 109, CS Doc B)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]				-	
[redacted]					
[redacted]					
[redacted]					

Abbreviations: ICER, incremental cost-effectiveness ratio, LYG, life year gained; QALY, quality-adjusted life year; SoC, standard-of-care.

Table 58. Results for patients with ASCVD and HeFH, with event probabilities from CPRD (Table 110, CS Doc B, pg 224)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio, LYG, life year gained; QALY, quality-adjusted life year; SoC, standard-of-care.

The ERG attempted to replicate results for this subgroup prior to conducting further scenario analysis based on CV event rates using data from the Beliard 2018 study.[74] However, results obtained by the ERG when using the CPRD event rate function within the model differed significantly resulting in an ICER of [redacted] (see Table 59). The ERG undertook technical checks of the model surrounding the relevant cells and inputs noting multiple errors. As the company's results could not be replicated, the ERG was also unable to conduct their preferred scenario analysis for this parameter.

Table 59. ERG results for patients with ASCVD and HeFH, with event probabilities from CPRD

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio, LYG, life year gained; QALY, quality-adjusted life year; SoC, standard-of-care.

5.3 *ERG's preferred assumptions*

Based on our concerns outlined in section 3.3.7, the ERG's preferred assumptions include making the following change to the company's base-case model (see. Table 60):

- Inclusion of ezetimibe as an active comparator.

Table 60: ERG's preferred model assumptions

Company base-case assumption	ERG preferred assumption	Section in this report
SoC comprises maximally tolerated statins with or without ezetimibe	Ezetimibe is an active comparator	In summary, ezetimibe inhabits the same position in the treatment pathway of hypercholesterolaemia as inclisiran is seeking marketing authorisation for, and is therefore an active comparator not just part of SoC. This is a deviation from the NICE final scope[81] where ezetimibe was listed an active comparator. This will likely have significant effect on the ICER for inclisiran, as now ezetimibe is available in generic form (since 2017/18), its cost effectiveness has increased. Full details are provided in Section 3.3.7

5.3.1 ERG base-case deterministic results

The ERG's base-case analysis includes ezetimibe + SoC as an active comparator in treating with ASCVD and PPER, with the deterministic results reported in Table 61 and Table 62, respectively.

Table 61. Deterministic results for the ASCVD population including ezetimibe as an active comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ASCVD, atherosclerotic cardiovascular disease, ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; SoC, standard of care

Table 62. Deterministic results for the PPER population including ezetimibe as an active comparator

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ICER, incremental cost-effectiveness ratio; PPER, primary prevention with elevated risk; QALY, quality adjusted life years; SoC, standard of care

The results show that for both ASCVD and PPER populations [redacted]

In the ASCVD population the ICER for inclisiran + SoC compared with ezetimibe + SoC is [redacted] per QALY and in the PPER population [redacted] per QALY. Additionally, the ERG noted a [redacted] in the ASCVD population [redacted] Similarly, a [redacted] was noted in the PPER population [redacted]

In Table 63, we present a summary of the company's deterministic base-case analysis results and the ERG's deterministic results to show the impact on the ICER, by including ezetimibe + SoC in the economic analysis. In summary, [redacted]

Table 63. Summary and impact of each change on the company's base-case ICERs

Population and scenario	ICER (£/QALY)	Change from base-case (%)
ASCVD		
Company' base-case	[redacted]	[redacted]
Inclusion of ezetimibe as an active comparator	[redacted]	[redacted]

Population and scenario	ICER (£/QALY)	Change from base-case (%)
PPER		
Company's base-case	[redacted]	[redacted]
Inclusion of ezetimibe as an active comparator	[redacted]	[redacted]
Primary prevention HeFH		
Company's base-case	[redacted]	[redacted]
Inclusion of ezetimibe as an active comparator	Analyses was not undertaken due to the paucity of information.	
ASCVD, atherosclerotic cardiovascular disease; ICER, incremental cost-effectiveness ratio; PPER, primary prevention with elevated risks		

5.3.2 ERG probabilistic sensitivity analysis results

The ERG were unable to undertake PSA on the results of their base-case due to multiple errors identified in the updated model provided by the company. The original model did not enable ezetimibe to be included as an active comparator therefore the ERG were not able to use this for the purpose.

5.4 *Conclusions of the cost effectiveness section*

The company's economic analysis was constructed using a Markov-cohort model programmed in Microsoft Excel, which was based on that submitted in TA393[68], and benefitted from structural improvements implemented as a result of recommendations made during the previous appraisal process[2]. The ERG considered that the type and structure of the submitted model was appropriate for use in the hypercholesterolaemia population and suitable for the decision problem in this appraisal. The model depicted the main features (progression to more severe post-CV event health state and time since CV event) for patients with hypercholesterolaemia.

The intervention and outcomes included in the company submission were as outlined by NICE. However, the ERG considered the comparators described in the CS deviated from those described in the NICE Final Scope[81] for treatment of people with hypercholesterolaemia. The marketing authorisation for inclisiran was for all people with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia, which is partially consistent with the evidence provided by the company. The company restricted the population to only hypercholesterolaemia patients with a **********[redacted]

The resource use and costs were in keeping with the viewpoint of the economic analysis, with information obtained from published sources and using current prices. Adherence was made to the NICE reference case[20] with regards model time horizon and discounting. To achieve a workable model the company made some simplifying assumptions, which the ERG found plausible.

Appropriate methods were used to identify information to populate the economic model, with the clinical information for inclisiran obtained from the ORION-9, -10 and -11 CSRs provided with the CS, and treatment efficacy derived from an NMA conducted by the company. In the absence of CV-outcomes data available from the ORION trials, a surrogate outcome was used which involved translating reduction in LDL-C levels to a reduction in CV event risks, with appropriate methodology used to adjust rates according to population baseline characteristics. The use of real world CPRD data (CS Document B, Appendix L) was relied upon for CV event risks in the UK population, which represent the population covered within this submission.

Under the company's assumptions and the economic model used, results for the 3 populations were reported:

- In the ASCVD population, inclisiran is [redacted] Results from the one-way sensitivity analyses showed that the base-case results were robust to univariate changes made to key input parameters except for [redacted] which had the greatest impact. The probabilistic sensitivity analysis suggested that at a £10,000 willingness-to-pay (WTP) threshold for a QALY, inclisiran had a [redacted] probability of being cost-effective when compared to SoC, and [redacted] probability at a £20,000 WTP threshold.
- In the PPER population, [redacted]
- In the primary prevention HeFH population, [redacted]

PSA results for all 3 populations indicated a good level of certainty in the ICERs presented and little variation with scenario analyses initially presented by the company.

Following concerns raised by the ERG during the clarification process regarding inclusion of ezetimibe as part of SoC, rather than being treated as an active comparator, the company provided the ERG with results of this as scenario analysis for the ASCVD and PPER populations. Results show, in both populations, [redacted] In the ASCVD population the ICER for inclisiran + SoC compared with ezetimibe + SoC is [redacted] per QALY and in the PPER population [redacted] per QALY. Results for the primary HeFH population could not be obtained as efficacy rates for ezetimibe from the NMA were not available for this population.

The ERG were satisfied that results of their additional scenario analysis on the mixed ASCVD population, using an alternative source of population weights, did not impact the ICER meaningfully and were confident to remain with the company's preferred source for their base-case.

Attempts made by the ERG to conduct a scenario analysis on the secondary HeFH subgroup, using CV event rates from a more recent source, were unsuccessful due to significant errors detected within the company model. These errors also prohibited replication of the company's scenario analysis so results could neither be validated, nor the most suitable source for CV event rates in this subgroup be established.

The ERG made one significant amendments to the company's economic model, which formed the basis for the ERG's base-case model. This change resulted in differences between the company's base-case results and those reported by the ERG. The company's results were presented based on using the PAS price for inclisiran and list prices for all other comparators, and formed the approach followed by the ERG in their analysis.

The ERG's amendment was inclusion of ezetimibe as an active comparator. Deterministic results for the ERG base-case are the same as those reported by the company in their scenario analysis. Ezetimibe treated as an active comparator [redacted]

The ERG were unable to undertake PSA on the results of their base-case due to multiple errors identified in the updated model provided by the company. Additionally, results for the primary HeFH population could not be obtained due to paucity of data surrounding efficacy of ezetimibe in this population. Results are therefore tentative, with further sensitivity analysis advised around the ERG's base-case

However, of the results that are presented, it should be noted that these were based on the PAS price for inclisiran and list prices for all other comparators; hence the analysis does not incorporate commercial agreements between the companies and the Department of Health for the other comparators.

6 END OF LIFE

There are no claims that end of life criteria apply to inclisiran in the company submission.

7 REFERENCES

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8 Appendix 1

ERG assessment of ORION-9 trial quality

NICE checklist item	*CS judgment and rationale*	*ERG judgment and rationale*
Selection bias		
Was randomization carried out appropriately?	Yes- low RoB "Randomization was stratified according to background use of statins with patients assigned (in a	Yes The CS and Raal et al 2020 report an automated interactive response technology (IRT) for randomly assigning patients. They were randomized 1:1 to receive an inclisiran or placebo. Treatment allocation was stratified in block sizes of 4 by 1) current use of statins or other lipid-lowering therapies (all three trials) and 2) country.[19]

	1:1 ratio) to receive either inclisiran (284 mg) or matching placebo.”	
Was the concealment of treatment allocation adequate?	Yes- low RoB “Randomization via automated interactive response technology (IRT) was used to assign subject to blinded investigational product kits”	Yes The CS has mentioned that an automated responsive technology (IRT) has been used for subject assignments. Placebo and inclisiran were both administered by 1.5 ml subcutaneous injection and packaged in the same container. Blinding of study drug was assured by the use of yellow shrouds applied to vials and syringes. The ERG finds the IRT method adequate for patient allocation.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes- low RoB “Randomization was stratified according to background use of statins. Other prognostic factors appeared balanced	Unclear Even though the company has announced that the baseline characteristics are well balanced but the ERG found no adjustments concerning the atherosclerotic cardiovascular disease subjects between the placebo and the inclisiran which is higher in the placebo group (no.: 73 vs 59) and might introduce some bias. Additionally, in table 2 (Raal et al 2020) the genetic variants are reported by treatment arm, and it is apparent within the study there are patients with pathogenic or likely pathogenic mutations, but also those with no variants (61/242 inclisiran [25.2%], 54/240 placebo [22.5%]) and those with no genetic testing (21/242 inclisiran [8.7%], 29/240 placebo [12.1%]). Those without a pathogenic mutation or testing, may not

	between arms”	classify as HeFH or be as likely to respond to treatment[19]
Overall rating of selection bias	NR	Some concern Based on the evidence that was provided by the company, classifying participants as HeFH without a pathogenic mutation or testing is considered high at risk of selection. Furthermore, no appropriate adjustments have been taken for ASCVD participants between the placebo and treatment.
Performance bias		
The comparison groups received the same care apart from the intervention(s) studied	NR	Unclear The CS reports that both the placebo and treatment arm have been blinded and both have gone under the same procedures. There is a list of permitted medications that and there is clear reporting of balance between placebo and inclisiran. [19, 90, 91]
Participants receiving care were kept 'blind' to treatment allocation	Yes- Low risk of bias “Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	Yes Double-blind randomization via an automated IRT was used to assign subjects to the blinded investigational product. Each vial contained a yellow shroud to ensure blinding.[19]

Individuals administering care were kept 'blind' to treatment allocation	Yes- Low risk of bias “Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	Yes The clinical study site pharmacist was maintained double-blind according to site-specific procedures and the Pharmacy Manual. It should be noted that inclisiran may be visually distinguishable from placebo; therefore, blinded syringes were provided to all study sites and used to maintain the blind. The investigational product was blinded before distribution to sites.[19]
Overall rating of performance bias	NR	Unclear Even though the company has gone through minimizing the performance bias, the ERG did not find sufficient evidence to support that groups were balanced. Moreover, concomitant permitted medications effect on study outcomes were found unclear.
Attrition bias		
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	NR	Yes Based on the CS, the end of study evaluations were conducted at the Day 540 visit for both placebo and inclisiran. Raal et al have reported that the end of study (EOS) visit was conducted on Day 540.[19]
The groups were	Low risk of	Yes

comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	bias “Discontinuation rate consistent across arms”	As the CS has reported, 4 placebo patients withdrew and 2 lost to follow-up. There were 5 for other reasons and 1 death and also 1 lost to follow-up for the inclisiran arm. 9 subjects out of 240 [3.8%] and 7 out of 242 [2.9%] could not finish the study. Therefore, outcome data were available and reported adequately.
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	NR	Yes The outcomes were available for most of the patients (241 inclisiran and 240 placeboes) and loss to follow-ups have not been considered in the CS analysis separately. Of the patients in the intention-to-treat population, 235 patients (91.7%) in the inclisiran group and 231 (96.3%) in the placebo group completed the trial activities through day 540.[19] No information provided on the characteristics of those for whom there is no outcome data.

Overall rating attrition bias	NR	Unclear Even though the discontinuation rate between groups was not found significantly different, the ERG could not collate further information concerning participants' characteristics who were withdrawn from the study.
Detection bias		
The study had an appropriate length of follow-up	NR	Yes The CS informs that the [redacted]
The study used a precise definition of outcome	NR	Yes The company has explained the outcomes of interest properly.
A valid and reliable method was used to determine the outcome	NR	Yes All efficacy parameters in the studies were laboratory assessments and were assessed in the fast state of subjects. Subjects were in a fast state for all clinical laboratory assessments. Screening laboratory tests were performed by a Good Laboratory practice accredited Central Laboratory. The high-sensitivity C-reactive protein (hsCRP) is performed routinely for safety throughout the study and is part of the central laboratory draws. Urinalysis evaluated by dipstick analyses at the investigational site (a standardized dipstick test was supplied by the Central Laboratory). Urinalysis was performed from a sample of mid-stream urine. In case of abnormal

		results, microscopy and other assessments were performed at the local laboratory, and the abnormality was recorded as an AE.[19]
Investigators were kept 'blind' to participants' exposure to the intervention	Yes- Low RoB “Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	Yes Raal et al report that the blinded syringes have been used by the care providers. The investigational product was blinded before distribution to sites. Study site pharmacists were maintained double-blind according to site-specific procedures and the Pharmacy Manual.[19]
Investigators were kept 'blind' to other important confounding and prognostic factors	Yes- Low RoB “Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	Unclear The ERG found no reports concerning investigators blinding to the prognostic and confounding factors. However, the ERG concluded that the investigators were blinded to the participants' intervention group.
Overall rating detection bias	NR	Unclear The company has provided proper considerations to reduce detection bias. Nonetheless, the ERG found no evidence to support the

		investigator's blindness to prognostic factors.
Questions listed on the company submission, not from the preferred NICE checklist		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes- low RoB "All pre-specified outcomes reported"	Yes The ERG found listed primary, secondary, and exploratory objectives and outcomes completely reported without missing.[19]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes- low RoB "All subjects randomized into the study comprised the intent-to-treat (ITT) population. Multiple imputation washout model was used to impute missing values for primary outcomes, control-based pattern mixture model was used to impute missing values for secondary	Yes Raal et al have used multiple imputation washout models for missing data. They have considered the intention-to-treat population for the primary efficacy analysis.[19] "The washout model was performed on actual values; change and percentage change values were calculated after the imputation" for missing data analysis. "In addition, sensitivity analyses using mixed-effect models for repeated measures (MMRM) without multiple imputations and a control-based pattern mixture model (PMM) was performed on the co-primary and key secondary efficacy endpoints to assess the impact of missing values."

	outcomes”	

ERG assessment of ORION-10 trial quality

NICE checklist item	*CS judgment and rationale*	*ERG judgment and rationale*
Selection bias		
Was randomization carried out appropriately?	Yes- low RoB “Subjects were randomized by an automated Interactive Response Technology (IRT) once subject eligibility was confirmed. Treatment allocation was stratified by current use of statins or other lipid-modifying therapies (LMT) in block sizes of 4.”	Yes Based on Ray et al 2020 ORION-10 RCT protocol as a double blind-study, an automated interactive response technology (IRT) has been used for randomly assigning patients. Treatment allocation was stratified by the current use of statins or other lipid-modifying therapies.[17]
Was the concealment of treatment allocation adequate?	Yes- low RoB “Subjects were randomized by an automated	Yes Subjects have been assigned to the blinded investigational product kits via automated interactive response technology (IRT). “Each vial and prefilled syringe, inclisiran or placebo,

	Interactive Response Technology (IRT)"	contained a yellow shroud to maintain the blinding. Blinded syringes were provided to all study sites to maintain the blind".[17]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes- low RoB "Randomization was stratified according to background use of statin. Other prognostic factors appeared balanced between arms"	Yes The ERG reviewed the CS and Ray et al RCT protocol and found the baseline and prognostic factors well balanced between arms. Moreover, the prognostic factors are well supported and reported for the placebo and treatment population.[17]
Overall rating of selection bias	NR	Low risk of bias
Performance bias		
The comparison groups received the same care apart from the intervention(s) studied	NR	Unclear Based on the Ray et al RCT protocol, the subjects, the clinical study site pharmacist and care providers have been blinded for the same procedures. However, the ERG found no evidence to support groups were balanced properly and no evidence to support permitted medications interfere with accurate interpretation of clinical trial was minimum.[17, 90, 91]

Participants receiving care were kept 'blind' to treatment allocation	Yes- Low risk of bias “Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	Yes Double-blind randomization via an automated IRT was used to assign subjects to the blinded investigational product. It is reported that blinded syringes with the same physical features have been used at the centers to maintain blinding.[17]
Individuals administering care were kept 'blind' to treatment allocation	Yes- Low risk of bias “Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	Yes The clinical study site pharmacist was maintained double-blind according to site-specific procedures and the Pharmacy Manual. It should be noted that inclisiran may be visually distinguishable from placebo; therefore, blinded syringes were provided to all study sites and used to maintain the blind. The investigational product was blinded before distribution to sites.[17]
Overall rating of performance bias	NR	Unclear Even though the company has gone through minimizing the performance bias, the ERG did not find sufficient evidence to support that groups were balanced. Moreover, concomitant permitted medications effect on study outcomes were found unclear.

Attrition bias		
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	NR	Yes The LDL-C assessment as a key objective has been continued till day 510. The end of the study has been reported the day 540 for both arms.[17]
The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes- Low RoB "Discontinuation rate consistent across arms"	Unclear As the CS has reported, comparable rates of completion across arms are as follows, 60/781 from the inclisiran arm withdrew (89% completion rate) compared to 85/780 from the placebo arm who withdrew (87% completion rate). The CS reports that "all retrieved data for patients who dropped out from study treatment were considered as non-missing data and utilized in all analyses". No information was provided on the characteristics of those who did not complete the study.
The groups were comparable with respect to the availability of	NR	Unclear The outcomes were available for most of the patients (781 inclisiran and 780 placebo) and dropouts have not been considered in the analysis. Of the patients in the intention-to-treat population, 781 in the inclisiran

outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).		group and 780 in the placebo group completed the trial activities through day 540.[17] No information is provided on the characteristics of those for whom there is no outcome data.
Overall rating attrition bias	NR	Unclear Even though the completion rates were almost the same for both groups, the characteristics of withdrawn participants were ambiguous and the ERG could not collate any information about them.
Detection bias		
The study had an appropriate length of follow-up	NR	Yes The CS informs that the [redacted]
The study used a precise definition of outcome	NR	Yes The company has explained the outcomes of interest properly.

A valid and reliable method was used to determine the outcome	NR	Yes All efficacy parameters in the studies were laboratory assessments and were assessed in the fast state of subjects. Subjects were in a fast state for all clinical laboratory assessments. Screening laboratory tests were performed by a Good Laboratory Practice accredited Central Laboratory. The hsCRP is performed routinely for safety throughout the study and is part of the central laboratory draws. Urinalysis evaluated by dipstick analyses at the investigational site (a standardized dipstick test was supplied by the Central Laboratory). Urinalysis was performed from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments were performed at the local laboratory, and the abnormality was recorded as an AE.[17]
Investigators were kept 'blind' to participants' exposure to the intervention	Yes- Low RoB “Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	Yes Ray et al report that the blinded syringes have been used by the care providers. The investigational product was blinded before distribution to sites. Study site pharmacists were maintained double-blind according to site-specific procedures and the Pharmacy Manual .[17]
Investigators were kept 'blind' to other important	Yes- Low RoB “Double-blind. Both treatments	Unclear The ERG found no reports concerning investigators blinding to the prognostic and confounding factors. However, the ERG concluded that

confounding and prognostic factors	dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	the investigators were blinded to the participants' intervention group.
Overall rating detection bias	NR	Unclear The company has provided proper considerations to reduce detection bias. Nonetheless, the ERG found no evidence to support the investigator's blindness to prognostic factors.
Questions listed on the company submission, not from the preferred NICE checklist		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes- low RoB “All pre-specified outcomes reported”	Yes The ERG found listed primary, secondary, and exploratory objectives and outcomes completely reported without missing.[17]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods	Yes- low RoB “An ITT population is used. All subjects randomized into the study comprised the ITT	Yes Ray et al have used multiple imputation washout models for missing data. They have considered the intention-to-treat population for the primary efficacy analysis. Mixed-effect models for repeated measures (MMRM) have been used on the percent change in LDL-C from baseline to Day 510 to test the superiority of inclisiran over placebo after missing data imputation. Missing data were imputed using multiple imputation washout models.

used to account for missing data?	Population. The first primary efficacy end point was analysed with the use of an analysis-of-covariance model, and the second primary efficacy end point was analysed with the use of a mixed model for repeated measures, both with multiple imputation of data"	Results were combined using Rubin's method.[17]

ERG assessment of ORION-11 trial quality

NICE checklist item	*CS judgment and rationale*	*ERG judgment and rationale*
Selection bias		
Was randomization carried out appropriately?	Yes- low RoB "Subjects were randomized by an automated Interactive Response Technology (IRT) only once subject eligibility was confirmed. Treatment allocation was stratified by country and by current use of statins or other lipid-modifying therapies (LMT) in block sizes of 4."	Yes Based on Ray et al 2020 ORION-11 protocol, it is a double-blind RCT and an automated interactive response technology (IRT) has been used for randomly assigning patients. Treatment allocation was stratified by current use of statins, other lipid-modifying therapies, and by country.[17]
Was the concealment of treatment allocation	Yes- low RoB "Subjects were	Yes Subjects have been assigned to the blinded

adequate?	randomized by an automated Interactive Response Technology (IRT)"	investigational product kits via automated interactive response technology (IRT).[17]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes- low RoB "Randomization was stratified according to background use of statins and country. Other prognostic factors appeared balanced between arms"	Yes The ERG reviewed the CS and Ray et al RCT protocol and found the baseline and prognostic factors well balanced between arms. Moreover, the confounders are well supported and reported for the placebo and treatment population.[17]
Overall rating of selection bias	NR	Low risk of bias
Performance bias		
The comparison groups received the same care apart from the	NR	Unclear Based on the Ray et al protocol concerning the ORION-11, the subjects, the clinical study site pharmacist and care providers have been blinded for the same procedures. However, the ERG found no evidence to support groups were balanced properly and no evidence to support

intervention(s) studied		permitted medications interfere with accurate interpretation of clinical trial was minimum..[17, 90, 91]
Participants receiving care were kept 'blind' to treatment allocation	Yes- Low RoB "Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions"	Yes Double-blind randomization via an automated IRT was used to assign subjects to the blinded investigational product. It is reported that blinded syringes with the same physical features have been applied at the centers to maintain blinding.[17]
Individuals administering care were kept 'blind' to treatment allocation	Yes- Low RoB "Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions"	Yes The clinical study site pharmacists were maintained double-blind according to site-specific procedures and the Pharmacy Manual. It should be noted that inclisiran may be visually distinguishable from placebo; therefore, blinded syringes were provided to all study sites and used to maintain blinding. The investigational product was blinded before distribution to sites.[17]
Overall rating of performance bias	NR	Unclear Even though the company has gone through minimizing the performance bias, the ERG did not find sufficient evidence to support that groups were balanced. Moreover, concomitant permitted medications effect on study outcomes were found unclear

Attrition bias		
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	NR	Yes The LDL-C assessment as a key objective has been continued till day 510. The end of the study has been reported the day 540.[17]
The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes- Low RoB "Discontinuation rate consistent across arms"	Unclear As the CS has reported, 770/807 (95%) of the placebo and 772 /810 (95%) of the inclisiran group have completed the study. The most common reasons for discontinuing the study were the withdrawal of consent (placebo-treated patients 17, inclisiran-treated patients 13); death (placebo-treated patients 15, inclisiran-treated patients 14); loss to follow-up (placebo-treated patients 3, inclisiran-treated patients 6); adverse events (placebo-treated patients 0, inclisiran-treated patients 4) and physician decision (placebo-treated patients 1, inclisiran-treated patients 1). The CS reports that "all retrieved data for patients who dropped out from study treatment were considered as non-missing data and utilized in all analyses". No information was provided on the characteristics of those who did not complete the study.
The groups were comparable with respect to the availability of	NR	Unclear The outcomes were available for most of the patients (810 inclisiran and 807 placebo) and dropouts have not been considered in the analysis. Of the patients in the intention-to-treat population, 810 in the inclisiran

outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).		group and 807 in the placebo group completed the trial activities through day 540 .[17] No information is provided on the characteristics of those for whom there is no outcome data.
Overall rating attrition bias	NR	Unclear Even though the completion rates were almost the same for both groups, the characteristics of withdrawn participants were ambiguous and the ERG could not collate any information about them.
Detection bias		
The study had an appropriate length of follow-up	NR	Yes The CS informs that the [redacted]
The study used a precise definition of outcome	NR	Yes The company has explained the outcomes of interest properly.

A valid and reliable method was used to determine the outcome	NR	Yes All efficacy parameters in the studies were laboratory assessments and were assessed in the fast state of subjects. Subjects were in a fast state for all clinical laboratory assessments. Screening laboratory tests were performed by a Good Laboratory Practice accredited Central Laboratory. The hsCRP is performed routinely for safety throughout the study and is part of the central laboratory draws. Urinalysis evaluated by dipstick analyses at the investigational site (a standardized dipstick test was supplied by the Central Laboratory). Urinalysis was performed from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments were performed at the local laboratory, and the abnormality was recorded as an AE.[17]
Investigators were kept 'blind' to participants' exposure to the intervention	Yes- Low RoB “Double-blind. Both treatments dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	Yes Ray et al report that the blinded syringes have been used by the care providers. The investigational product was blinded before distribution to sites. The study site pharmacist was maintained double-blind according to site-specific procedures and the Pharmacy Manual.[17]
Investigators were kept 'blind' to other important	Yes- Low RoB “Double-blind. Both treatments	Unclear The ERG found no reports concerning investigators blinding to the prognostic and confounding factors. However, the ERG concluded that

confounding and prognostic factors	dispensed and administered as a 1.5ml subcutaneous injection under blinded conditions”	the investigators were blinded to the participants' intervention group.
Overall rating detection bias	NR	Unclear The company has provided proper considerations to reduce detection bias. Nonetheless, the ERG found no evidence to support the investigator's blindness to prognostic factors.
Questions listed on the company submission, not from the preferred NICE checklist		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes- low RoB “All pre-specified outcomes reported”	Yes The ERG found listed primary, secondary, and exploratory objectives and outcomes completely reported without missing.[17]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to	Yes- low RoB “An ITT population is used. All subjects randomized into the study comprised the ITT Population.	Yes Ray et al have used multiple imputation washout models for missing data. They have considered the intention-to-treat population for the primary efficacy assessment by considering the analysis-of-covariance model. Mixed-effect models for repeated measures (MMRM) have been used on the percent change in LDL-C from baseline to Day 510 to test the superiority of inclisiran over placebo after missing data imputation. Missing data were imputed using multiple imputation washout models.

account for missing data?	The first primary efficacy end point was analysed with the use of an analysis-of-covariance model, and the second primary efficacy end point was analysed with the use of a mixed model for repeated measures, both with multiple imputation of data."	Results were combined using Rubin's method.[17]

Table 64. Summary of cost-effectiveness study retrieved following company SR

Study	Country and perspectiv	Summary of model	Patient population	QALYs, Costs (intervention, comparator) and ICER per QALY gained	Applicability to decision

	e				**making in England**
Patient population: ASCVD					
Kam et al 2020 [67]	Australian healthcare system perspective for CUA	Cost utility analysis comparing the combination of Statin + Inclisiran treatment to Statin+/- Ezitimibe A cohort-based Markov decision analytic model was developed with a lifetime time horizon and 1 year cycle length Clinical data was obtained from Orion 10 clinical trial Costs were obtained from published sources Costs were expressed in $ (cost year, 2020) Both costs and QALY were discounted at 5% per year	Patients with ASCVD beginning at age 66-year	Intervention: Inclisiran + statin (+/- Ezitimibe) Comparator: Statin (+/- Ezitimibe) ICER Cost/ QALY: $125,732 Results were not cost effective from the Australian health care perspective with WTP AU$50,000. Drug costs would need to be reduced by 60% at this threshold. 0.468 QALYs per person at drug acquisition cost $6,334	Applicable for Australia as evaluation was set in Australian health system perspective

9 Appendix 2

ERG Cost effectiveness PSA results using company base case

Table 65. Results of company probabilistic sensitivity analysis, PPER

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.

Table 66. Results of ERG probabilistic sensitivity analysis, PPER

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Table 67. Results of company probabilistic sensitivity analysis, primary prevention HeFH

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

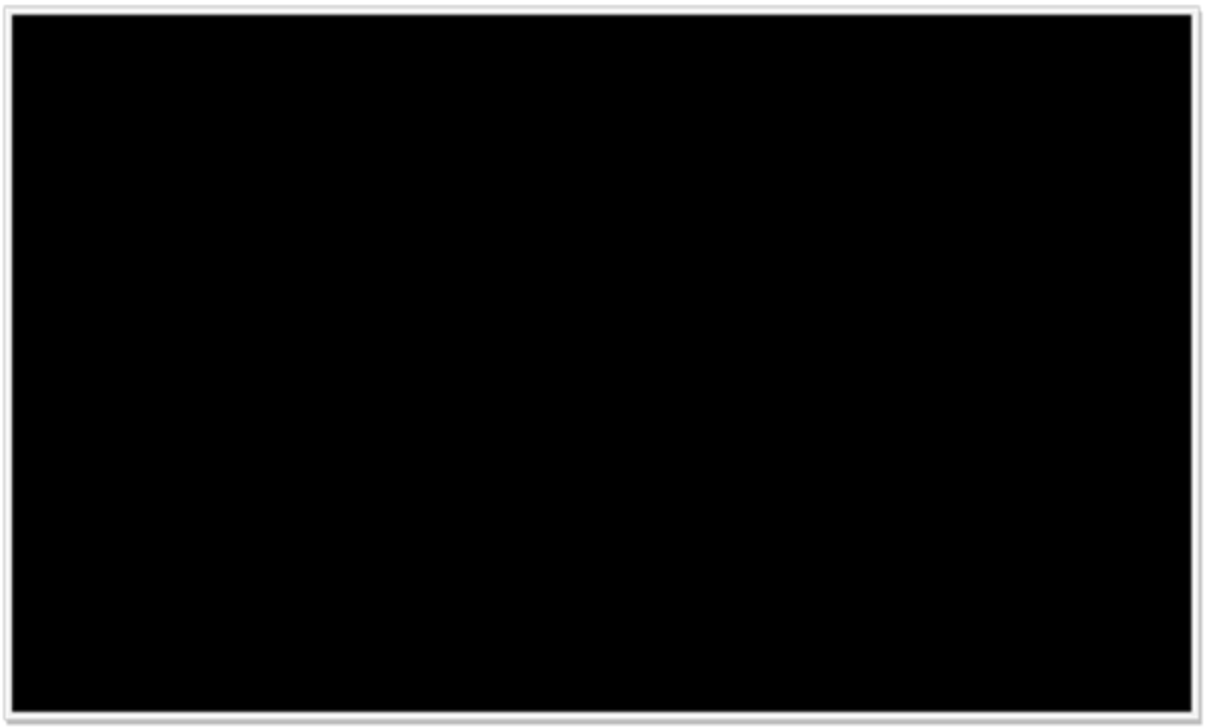
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of car

Table 68. Results of ERG probabilistic sensitivity analysis, primary prevention HeFH

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SoC, standard of care.



[redacted]