NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from Novartis
2. **Clarification questions and company responses**
3. **Additional clarification questions and company responses**
4. **Patient group, professional group, and NHS organisation submissions** from:
   a. HEART UK
5. **Evidence Review Group report** prepared by Warwick Evidence
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Post-technical engagement documents

7. **Technical engagement response from company:**
   a. Response form
   b. Appendix 1
   c. Appendix 2
   d. Appendix 3
   e. Results for PCSK9i eligible and ineligible patients – requested by NICE technical team
8. **Technical engagement responses from experts:**
   a. Alan Jones, Consultant Physician – clinical expert, nominated by Sanofi
   b. Kausik Ray, Professor of Public Health and Honorary Consultant Cardiologist – clinical expert, nominated by Novartis
9. **Technical engagement responses from consultees and commentators:**
   a. HEART UK
   b. British Cardiovascular Society – endorsed by Royal College of Physicians

c. Primary Care Cardiovascular Society
d. Amgen
e. Daiichi Sankyo

10. Evidence Review Group critique of company response to technical engagement prepared by Warwick Evidence**:**
a. Main critique
b. ERG appendix 5

11. Company price revision information from Novartis

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Document B

Company evidence submission

October 2020

File name	Version	Contains confidential information	Date
ID1647 inclisiran Document B Fully Redacted	1.0	Yes	30/10/20

Contents

Tables and figures

Abbreviations

Acronym	Definition
ACC	American College of Cardiology
ACS	Acute coronary syndrome
ACEi	Angiotensin-converting-enzyme inhibitors
AHA	American Heart Association
ANCOVA	Analysis of covariance
Apo B	Apolipoprotein B
ARB	Angiotensin II receptor blockers
ASCVD	Atherosclerotic cardiovascular disease
ASCVD-RE	Atherosclerotic cardiovascular disease risk-equivalent
BNF	British National Formulary
CHD	Coronary heart disease
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CTT	Cholesterol Treatment Trialists
CV	Cardiovascular
CVD	Cardiovascular disease
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
EQ-5D	EuroQol-five dimensions
ERG	Evidence review group
ESC	European Society of Cardiology
FAS	Full analysis set
FH	Familial hypercholesterolaemia
GalNAc	Conjugated with triantennary N-acetylgalactosamine
HADS-A	Hospital Anxiety and Depression Scale - Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Depression
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
HRQoL	Health-related quality of life
IS	Ischaemic stroke
ITT	Intention-to-treat

Acronym	Definition
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein-cholesterol
LLT	Lipid lowering therapy
LSM	Least squares mean
MACE	Major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified intention-to-treat
MMRM	Mixed-effect models for repeated measures
mRNA	Messenger RNA
NF	Non-fatal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
OR	Odds ratio
PAD	Peripheral arterial disease
PAS	Patient access scheme
PCSK9	Proprotein convertase subtilisin/kexin type 9
PMM	Pattern mixture model
PPER	Primary prevention with elevated risk
PYs	Person-years
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
REML	Restricted Maximum Likelihood
RISC	Ribonucleic acid-induced silencing complex
RR	Rate ratio
siRNA	Small interfering ribonucleic acid
SLR	Systematic literature review
SoC	Standard-of-care
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIA	Transient ischaemic attack
UA	Unstable angina

Acronym	Definition
VLDL-C	Very-low-density lipoprotein-cholesterol

B.1 Decision problem, description of the technology and clinical care pathway

Disease overview

- Hypercholesterolaemia refers to elevated levels of cholesterol in the blood, including low-density lipoprotein cholesterol (LDL-C) (1)
    - Familial hypercholesterolaemia (FH) is an autosomal dominant disorder typically caused by mutations in one of three genes involved in LDL-C metabolism (2, 3)
    - Non-FH has no specific genetic cause and is likely caused by the interaction of several genes, in conjunction with dietary and other factors such as smoking or physical inactivity (4)
- Long-term elevations in LDL-C accelerate atherosclerosis, increasing the risk of developing atherosclerotic cardiovascular disease (ASCVD). Evidence from genetic studies, prospective epidemiologic cohort studies, Mendelian randomisation studies, and randomised clinical trials of LDL-lowering therapies all demonstrate a consistent dose-dependent log-linear association between the absolute magnitude of exposure to LDL-C and the risk of ASCVD, with risk increasing with duration of exposure (5)

Hypercholesterolaemia and ASCVD represent a substantial clinical, humanistic and economic burden

- Almost half of UK adults are living with cholesterol levels exceeding national guideline recommendations (total cholesterol >5 mmol/L) (6)
- Atherosclerotic cardiovascular disease is one of the UK's leading causes of death, and 4.7 million individuals are living with ASCVD in the UK (6, 7)
- Although cardiovascular (CV) events are often acute (such as myocardial infarction [MI] or stroke), they can be followed by a lengthy period of recovery during which recurrent events may also occur (8); the impact on health-related quality of life (HRQoL) is therefore generally prolonged, following the course of recovery. In some patients a full recovery is not possible, resulting in a lasting impact

- Healthcare costs for ASCVD amount to £9 billion per year in the UK, and the total economic impact (including indirect costs) is estimated to be £19 billion per year (6)

An unmet need remains for treatments that reduce LDL-C levels beyond the reductions obtained with statins

- Hypercholesterolaemia is treated with lifestyle modifications (including dietary changes, exercise, and smoking cessation) and lipid modification therapies, primarily high intensity statins (9)
- However, even well-managed ASCVD patients may still not reach guideline-recommended LDL-C levels (10)
- Monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) are recommended when LDL-C levels are persistently above specific thresholds despite maximum tolerated lipid-lowering therapy (11, 12)
- PCSK9 inhibitors have been shown to reduce LDL-C levels by more than 50% (13, 14), however they require subcutaneous administration every 2 to 4 weeks and may be associated with sub-optimal adherence (15).

Inclisiran offers the potential for sustained reductions in LDL-C levels with a twice-yearly dosing regimen

- Inclisiran selectively and effectively degrades the messenger ribonucleic acid (mRNA) encoding PCSK9, reducing circulating LDL-C levels by ≥50% (placebo-adjusted) by Day 510 in clinical trials (Section B.2)
- Inclisiran is anticipated to be licensed for 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 who are 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 (16).
- CHMP positive opinion was received on 15 October 2020

- Inclisiran will be administered twice-yearly by a healthcare professional (following initial dosing at day 0, and at 3 months)
- The combination of inclisiran's efficacy (Section B.2) and twice-yearly maintenance dosing means that the treatment offers the potential to help patients reach their LDL-C goals with minimal administration requirements for the healthcare system. This may lead to better adherence in the management of hypercholesterolaemia, with minimal burden on the healthcare system.

B.1.1 Decision problem

Inclisiran is anticipated to be licensed for 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 who are 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 (16).

This submission focuses on part of the technology's marketing authorisation:

- 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 (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 encompassing people who are at elevated risk for a range of reasons (including HeFH), while the HeFH group are at elevated risk specifically due to HeFH.

These populations are most aligned with the evidence base for inclisiran. They are expected to be the populations in which the greatest clinical benefits are observed, and in which inclisiran is most cost-effective. This view is supported by clinical expert opinion; further details are provided in Table 1 and Section B.1.3.5.

The company submission is generally consistent with the final NICE scope and the NICE reference case, with differences outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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 (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 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 (17) and the clinical trial write-up in Section B.2, primary prevention patients with elevated risk are referred to as 'ASCVD 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 anticipated 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 (18). Therefore, inclisiran is expected to provide the greatest clinical benefit in this population. This threshold has historically been considered a threshold for up-titration and add-on therapy for PCSK9 inhibitors (19), 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). 

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		equivalents'. This term is synonymous with the term 'primary prevention with elevated risk' used elsewhere in this dossier.	[redacted]
Intervention	Inclisiran, alone or with a statin, with or without other lipid-lowering therapy	As per final scope.	Not applicable.

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

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope

	• When maximally tolerated statin dose does not appropriately control LDL-C:
	  ○ Ezetimibe with a statin
	  ○ Evolocumab with a statin (with or without another lipid-lowering therapy)
	  ○ Alirocumab with a statin (with or without another lipid-lowering therapy)
	• When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C:
	  ○ Ezetimibe with a statin (when evolocumab and alirocumab are not appropriate)
	  ○ Evolocumab with a statin (with or without another lipid-lowering therapy)
	  ○ Alirocumab with a statin (with or without another lipid-lowering therapy)
	  ○ Bempedoic acid with a statin (subject to ongoing NICE appraisal)
	  ○ Bempedoic acid in a fixed dose combination with ezetimibe, alone or with a
		○ Evolocumab (with or without another lipid-lowering therapy)
		○ Alirocumab (with or without another lipid-lowering therapy)	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	statin (subject to ongoing NICE appraisal).		
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" (12).
Subgroups to be considered	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 ○ with HeFH ○ serum LDL-C ≥4.0 mmol/L ○ serum LDL-C ≥3.5 mmol/L and who are very high risk ○ statin intolerance • primary prevention for those with elevated risk	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 (see 'Population' section), 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

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		○ statin intolerance • primary prevention for adults with HeFH ○ serum LDL-C ≥4.0 mmol/L ○ serum LDL-C ≥5.0 mmol/L ○ statin intolerance	alirocumab and evolocumab (11, 12). 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 clinical trial programme, across which [redacted] ([redacted]) of ASCVD patients were statin intolerant (21)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia LDL-C; low density lipoprotein-c; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PPER, primary prevention with elevated risk.

B.1.2 Description of the technology being appraised

In appendix C include the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

Table 2: Technology being appraised

UK approved name and brand name	Inclisiran (Leqvio®)
Mechanism of action	Inclisiran is a double-stranded small interfering RNA, conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, the antisense strand is incorporated in the RNA-induced silencing complex (RISC) and directs catalytic breakdown of mRNA for PCSK9, thereby inhibiting translation of PCSK9 protein. The reduction of intrahepatic PCSK9 levels increases LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C levels in the circulation.
Marketing authorisation/CE mark status	Inclisiran does not yet have marketing authorisation for the indication in the submission. A regulatory submission was made to the EMA in January 2020. CHMP positive opinion was received on 15 October 2020 and marketing authorisation is expected to be granted by the European Commission in December 2020.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Inclisiran is anticipated to be licensed for 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 (16).
Method of administration and dosage	Inclisiran is delivered via subcutaneous injection. Injections should not be given into areas of active skin disease or injury such as sunburns, skin rashes, inflammation or skin infections. Inclisiran is intended for administration by a healthcare professional. The recommended dosage is 284 mg administered as a single subcutaneous injection: initially, again at 3 months and then every 6 months. Each 284 mg dose is administered using a single pre-filled syringe.
Additional tests or investigations	No additional tests or investigations are expected above and beyond what is routine clinical practice in this patient population.

List price and average cost of a course of treatment	The list price is £1,987.36 per 284 mg dose pack. The first year of treatment costs [redacted] (list/commercial price) per patient; subsequent years cost [redacted] per patient.
Patient access scheme (if applicable)	Inclisiran is available at a cost of [redacted] per 284 mg dose via a confidential commercial access agreement.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHMP, Committee for Medicinal Products for Human use; EMA, European Medicines Agency; LDL-C, low density lipoprotein-c; mRNA, messenger ribonucleic acid; PCSK9, proprotein convertase subtilisin/kexin type 9; RNA, ribonucleic acid.

B.1.3 Health condition and position of the technology in the treatment pathway

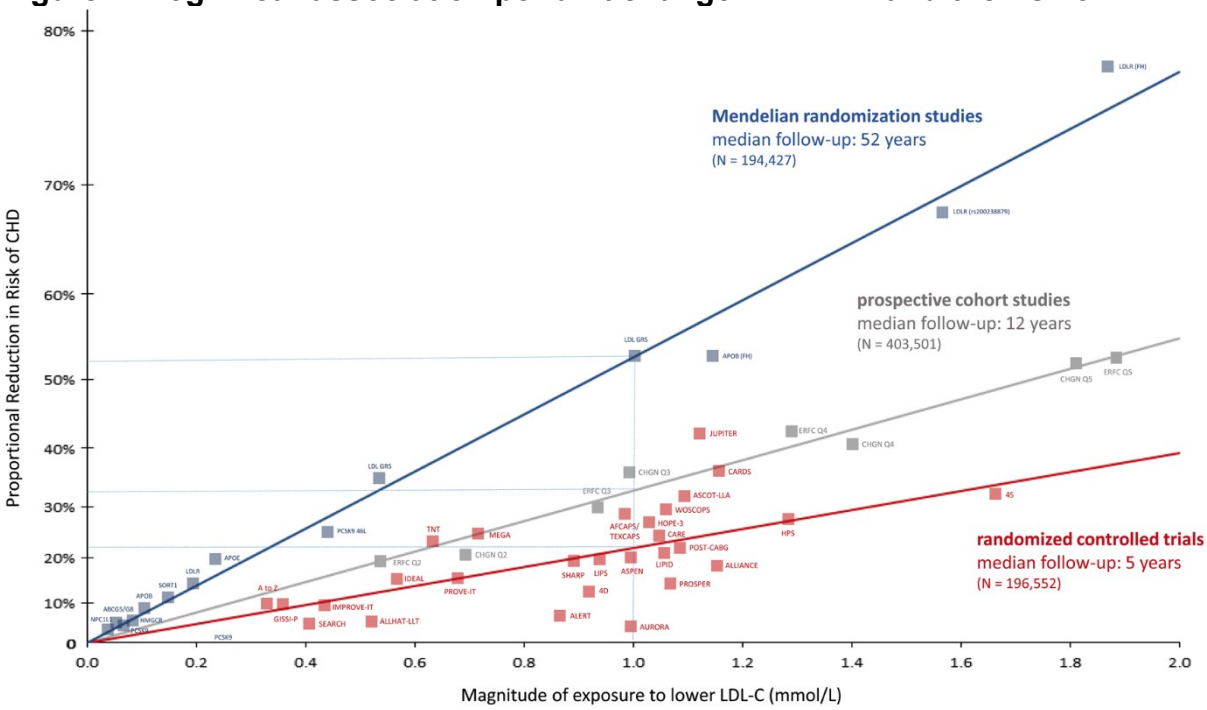
B.1.3.1 Disease overview

Hypercholesterolaemia is defined as the presence of elevated levels of cholesterol in the blood, typically including low-density lipoprotein cholesterol (LDL-C) (1). When elevated LDL-C levels are accompanied by increased triglyceride levels and decreased high-density lipoprotein cholesterol (HDL-C) levels, it is referred to as mixed dyslipidaemia.

Lipoproteins are complex aggregates of lipids and proteins that circulate in the bloodstream. Their predominant function is to transport lipids, mainly cholesterol and triglycerides, to the cells and tissues of the body. Excessive levels of LDL-C lead to a build-up of fatty material (plaques or atheroma) on the walls of arteries – a process known as atherosclerosis. The resulting hardening and narrowing of the arteries restricts blood flow and oxygen supply to vital organs, and increases the risk of blood clot formation (22).

Cardiovascular disease (CVD) is comprised of atherosclerotic cardiovascular disease (ASCVD), and non-ASCVD (23). LDL-C is the major causal risk factor for ASCVD (5): A 2017 consensus statement from the European Atherosclerosis Society Consensus Panel assessed the totality of evidence from genetic studies, prospective epidemiologic cohort studies, Mendelian randomisation studies, and randomised trials of LDL-lowering therapies (5). The evidence demonstrates a consistent dose-dependent log-linear association between the absolute magnitude of exposure to LDL-C and the risk of ASCVD, with risk increasing with duration of exposure (Figure 1). The panel were satisfied that all criteria for causality were met.

Figure 1: Log-linear association per unit change in LDL-C and the risk of CHD



Source: Ference et al 2017 (5)
Abbreviations: CHD, coronary heart disease; LDL-C, low density lipoprotein cholesterol.

Symptoms do not usually develop until significant atherosclerosis has developed and a cardiovascular (CV) event (such as a heart attack or stroke) has occurred.

Although LDL-C is known to be a major causal risk factor for cardiovascular disease and is regularly used in literature, high levels of non-HDL-C are also associated with long-term risk of ASCVD (24). There is increasing recognition amongst medical experts and opinion leaders that there are inconsistencies across England in how atherosclerosis and CV risk are actually measured. In day-to-day clinical practice, it is widely acknowledged that health care professionals use measures such as LDL-C calculated from a total cholesterol reading and more commonly, they may use non-HDL-C instead to assess risk. [redacted] stated, “My own preference is to order all tests on the lipid panel (e.g. Non-HDL-C, TG, HDL, LDL-C (calculated)). My local lab report the non-HDL-C and LDL-C (calculated) but many labs in the UK do not. I do not advocate the use of fasting LDL-C test as standard, I will only suggest this when a patient has very high triglyceride levels on a non-fasted sample. Every patient who needs a lipid assessment should have at least a LDL-C and/or non-HDL-C measured, but I am more familiar with LDL-C measurements and interpretation of this result in clinical practice”

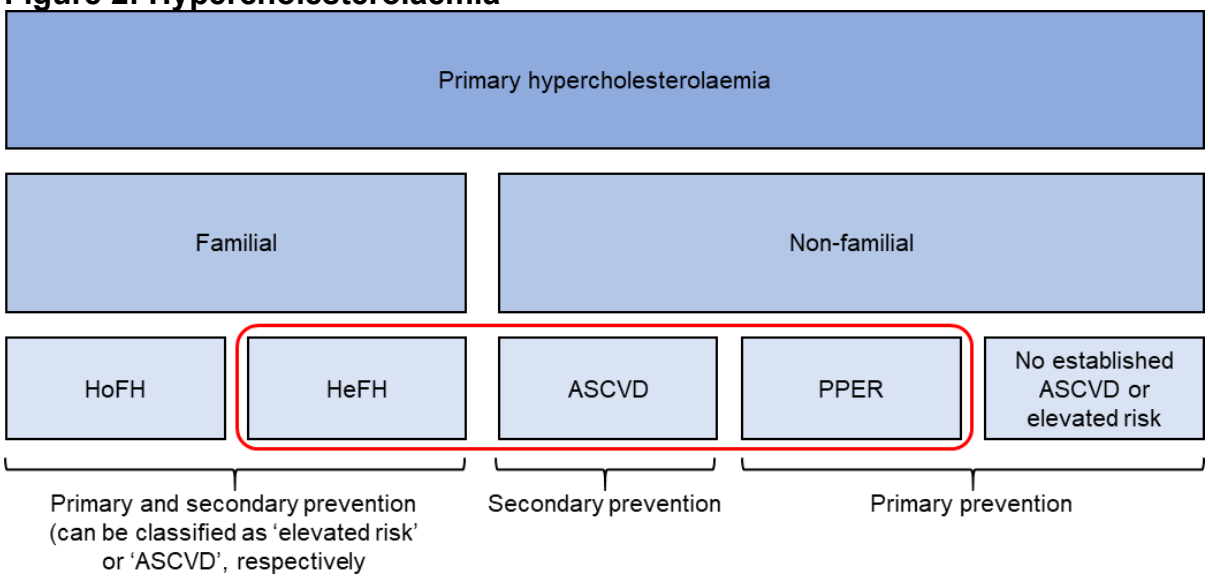
Using these measures in place of a fasting LDL-C test is increasingly common but it is also recognised by medical experts in lipid management as a practical approach, especially in primary care where time is constrained. This was further validated by [redacted] who stated, “To accurately assess cardiovascular risk, a fasting LDL-C together with a non HDL-C would be ideal. However, it is not often practical to obtain a fasting sample from patients and I believe it to be generally acceptable in these scenarios to use a non-fasting LDL-C measurement to calculate risk”. The inconvenience of fasting for patients also needs to be considered, and when appropriate fasting does not take place it can cause inaccuracies in the results.

When considering specifically the initiation of new LDL-C lowering therapies, [redacted] stated "LDL-C levels would be calculated from Total Cholesterol/Triglycerides/HDL-C and not a specific LDL-C measurement. The results from the lipid panel should be from the last 3 months and if not another lipid panel would be requested”.

B.1.3.2 Familial and non-familial hypercholesterolaemia

Hypercholesterolaemia can be broadly divided into familial and non-familial disease (Figure 2). This submission focuses on the populations outlined in red (described in Table 1) to reflect the available clinical evidence.

Figure 2: Hypercholesterolaemia



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; PPER, primary prevention with elevated risk.

B.1.3.2.1 *Familial hypercholesterolaemia*

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder, with approximately 90% of cases associated with mutations in one of three specific genes associated with the metabolism of LDL-C (2, 3).

Most people with FH have the heterozygous form (HeFH) and possess one copy of the defective gene. Life-long cumulative exposure to highly elevated levels of serum LDL-C (typically defined as LDL-C >4.9 mmol/l) accelerates the development of atherosclerosis and drives early onset ASCVD. Myocardial infarctions (MI) – often the first manifestation of FH – can occur as early as the third decade of life, approximately 20 years earlier than patients without FH (2, 25). If untreated, 50% of men and 30% of women with FH develop coronary heart disease by the age of 50 years (3, 26).

A small proportion of patients have the homozygous form (HoFH; outside the indication for inclisiran) in which both copies of the defective gene are affected (27). Homozygous FH is particularly rare, with an estimated prevalence in the UK of 1 in 1,000,000 individuals (28).

As shown in Figure 2, people with FH may be considered to be either a primary prevention population with elevated risk (PPER, i.e. 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 (i.e. those who have already experienced an ASCVD event).

B.1.3.2.2 *Non-familial hypercholesterolaemia*

Non-familial hypercholesterolaemia (non-FH) has no specific genetic cause and is likely to be caused by the interaction of several genes in conjunction with dietary and other lifestyle factors such as smoking or physical inactivity (4).

Hypercholesterolaemia in patients with non-FH is largely asymptomatic until the development of symptomatic atherosclerotic cardiovascular disease (ASCVD), such as such as angina, myocardial infarction, transient ischaemic attacks, or stroke, and claudication (1). Recommendations for the assessment of ASCVD risk relate to both

primary prevention (reducing risk in patients who have not experienced a prior CV event) and secondary prevention (reducing the risk of further events in patients who have already experienced a CV event).

B.1.3.2.3 *Overlap of FH and ASCVD populations*

It should be noted that whilst Figure 2 appears to show distinctly separate populations, there is an overlap between the FH and ASCVD populations. As described in Section B.1.3.2.1, patients with FH are characterised by highly elevated levels of serum LDL-C and a very high cumulative exposure from birth onwards. This is associated with an accelerated development of atherosclerosis and drives early onset of ASCVD.

As a result, FH patients with no other major risk factors who have not yet experienced an event - the 'FH primary prevention patients' - are considered 'high risk' or 'very high risk' as determined by both ESC/EAS and AHA/AAC guidelines (29, 30). Therefore, this group falls into the 'primary prevention with elevated risk factors population' (Section B.1.3.2.4) referred to in this submission, which is synonymous with the 'ASCVD risk-equivalent population' described in the ORION-10 and ORION-11 publication and defined as either FH, type 2 diabetes, or 10-year risk of a CV event ≥20% (assessed by Framingham risk score) (17).

Some FH patients go on to experience an event and therefore become categorised as ASCVD patients, which results in a clinical overlap. However, their original aetiology remains FH and they are inherently considered 'secondary prevention FH patients'.

B.1.3.2.4 *Primary prevention in patients with elevated risk*

Risk calculator algorithms have been developed to estimate an individual's risk of developing an ASCVD event over the next 10 years (31, 32). These algorithms have been validated in a primary prevention population and may be used to direct treatment decisions for people who are at high risk or very high risk of an event, but have not yet experienced any event.

There is a lack of consensus in the defining characteristics of different risk categories between international guidelines, clinical trials, and regulatory agencies. The criteria for ‘very high risk’ and ‘high risk’ patients does include the relevant primary prevention with elevated risk factors group seen in ORION-11. The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) and 2018 American Heart Association (AHA)/American College of Cardiology (ACC) definitions of high and very high-risk states are presented in Table 3 (29, 30). These guidelines are applicable across primary and secondary prevention, and the variation between guidelines illustrates the need for clarity when defining populations based on elevated risk factors. For example, peripheral arterial disease (PAD) is notably documented as an elevated risk factor for primary prevention in the ESC/EAS guidelines. However, in the AHA/ACC guidelines and in the Phase 3 ORION-11 trial (Section B.2.3.3.1) it is considered part of ASCVD.

Table 3: Risk categories as defined in the 2019 ESC/EAS guidelines and 2018 AHA/ACC guidelines

Category	ESC/EAS criteria	AHA/ACC criteria
Very high-risk	• Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG, and other arterial revascularisation procedures), stroke and TIA, and PAD. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. • DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years)	• Very high risk includes a history of multiple major ASCVD events: o recent ACS within 12 months o history of MI other than recent ACS o history of IS o symptomatic PAD (ABI<0.85 or previous revascularisation or claudication) • or 1 major ASCVD event and multiple high-risk conditions

Category	ESC/EAS criteria	AHA/ACC criteria
	• Severe CKD (eGFR <30ml/min/1.73 m^2) • A calculated SCORE ≥10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor	
High risk	• Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dl), LDL-C >4.9 mmol/L (>190 mg/dl), or BP ≥180/110 mmHg • Patients with FH without other major risk factors • Patients with DM without target organ damage with DM duration ≥10 years or another additional risk factor • Moderate CKD (eGFR 30–59 ml/min/1.73 m^2) • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD	• Age ≥65y • HeFH • History of prior CABG or PCI outside of major ASCVD event • Diabetes • Hypertension • CKD (eGFR 15-59 ml/min/1.73m^2) • Current smoking • Persistently elevated LDL-C (>100mg/dl [2.59 mmol/l] despite maximally tolerated statin and ezetimibe) • History of congestive HF

Source: Mach et al 2020 (29) and Grundy et al 2019 (30)
Abbreviations: ABI, ankle-brachial index; ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CT, computerised tomography; CVD, cardiovascular disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; LDL-C, low density lipoprotein-cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SCORE, Systematic COronary Risk Evaluation; T1DM, type 1 diabetes mellitus; TC, total cholesterol; TIA, transient ischaemic attack.

B.1.3.3 Epidemiology

B.1.3.3.1 *Hypercholesterolaemia*

Almost half of UK adults are living with cholesterol levels exceeding national guideline recommendations (total cholesterol >5 mmol/L); this proportion is even higher when considering individuals with ASCVD who have lower recommended limits (6).

B.1.3.3.2 *Atherosclerotic cardiovascular disease*

An estimated 4.7 million individuals are living with ASCVD in the UK, with numbers expected to rise due to the ageing population and improved survival following CV events (6, 7).

Reducing the risk of CVD over the next decade is a focus of Public Health England and NHS England (33). Cardiovascular disease is one of the UK's leading causes of death, with 170,000 deaths per year (one quarter of all deaths) (34). Approximately 4 in 5 of all CVD deaths are due to ASCVD (35).

It is estimated that 1.1 million adults in England have ASCVD and LDL-C levels ≥2.6 mmol/L, despite receiving statins and/or ezetimibe (7).

B.1.3.3.3 *Primary prevention in individuals with elevated risk*

Approximately 8.2 million individuals in the UK are estimated to be at elevated risk of developing ASCVD corresponding to approximately 6.9 million in England; of these, 5.3 million are receiving lipid-lowering therapies, corresponding to approximately 4.2 million in England (7).

It is estimated that 1.5 million adults at elevated risk of developing ASCVD in England have LDL-C levels ≥2.6 mmol/L, despite receiving statins and/or ezetimibe (7).

B.1.3.3.4 *Familial hypercholesterolaemia (primary and secondary prevention)*

Familial hypercholesterolaemia is estimated to affect 1 in 311 people (36).

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 (36).

B.1.3.4 Burden of disease

B.1.3.4.1 *Clinical burden*

Hypercholesterolaemia itself is asymptomatic, but the resulting formation of atherosclerotic plaques can lead to a range of CV events that can lead to severe

disability, and even death. Atherosclerotic cardiovascular disease is the leading cause of death and disability worldwide and is expected to remain so beyond 2040 (37). Thus, lowering LDL-C represents a significant opportunity to impact overall mortality.

Familial hypercholesterolaemia is associated with a significant clinical burden, with mortality rates 2.5-fold higher than the general UK population (38). Compared with the general population, FH was found to be associated with a 2.5- to 9-fold increase in the risk of CV events in the UK (38, 39).

The clinical burden is also substantial for patients with ASCVD; the all-cause mortality rate in a cohort of UK patients who had experienced a CV event was found to be 28.5 per 100 person-years (PYs) in the 6 months following the first CV event, rising to 36.5 per 100 PYs following the second event (40). The risk of CV events also increases following prior events; in another UK study, one-third of patients experienced a subsequent CV event over 5 years of follow-up (41).

B.1.3.4.2 *Humanistic burden*

Although cardiovascular events are often acute (such as MI or stroke), they can be followed by a lengthy period of recovery during which recurrent events may also occur; around 47% of patients have a further acute event on average within 114 days (8). The impact on health-related quality of life (HRQoL) is therefore generally prolonged, following the course of recovery. In some patients a full recovery is not possible, resulting in a lasting impact. Recurrent events in particular have a substantial humanistic burden because they can have a cumulative impact on patients' HRQoL, with studies demonstrating worse HRQoL in patients with recurrent events (42-44).

In a UK study of 9,566 patients who had survived an MI, over two-thirds of patients (69.1%) reported experiencing an impairment in one or more domains of the EuroQol-five dimensions (EQ-5D) during hospitalisation, and 59.7% reported impairment at 12 months (44). The activities domain was most affected, with 50% and 58.5% of patients reporting impairment at hospitalisation and after 30 days, respectively. Most patients reported improvements in average EQ-5D scores over

the year following the event (68.1%), although 22.1% had no improvement and 9.8% reported worsening scores.

Similarly, in a UK study of 748 patients who had experienced a stroke, and 404 patients who had experienced a transient ischaemic attack (TIA), mean utility was significantly lower at 1 month following a stroke compared with a cohort of the general population with matched characteristics (0.61 vs 0.85; p<0.001) (45). Events of worse severity and a higher number of recurrent events both significantly predicted decreased long-term utility. Over time, mean utility across all patients improved slightly following a stroke, from 0.64 after 1 month to 0.70 after 6 months (p=0.006) and remained at approximately 0.70.

B.1.3.4.3 *Caregiver burden*

Survivors of CV events may require support from informal caregivers, which can lead to a detrimental impact on the quality of life of individuals providing such support. Indeed, a UK study of 232 caregivers of patients who had experienced a stroke found caregiver burden to be high: mean caregiver burden score[a] was 48.2 in the 3 months after a stroke, improving to 38.3 at 1 year after the stroke (p<0.0001; higher scores indicate greater burden) (46). Anxiety and depression, as assessed by the Hospital Anxiety Score (HADS-A) and the Hospital Depression Score (HADS-D)[b], also improved from 3 months to 1 year after the stroke (HADS-A: from 6.0 to 3.0; HADS-D: from 4.0 to 2.0; p<0.0001 for both). The authors suggest that this improvement may occur as caregivers adapt to their new role. However, no change in caregiver HRQoL (measured using EQ-VAS) was seen in the 3 months to 1 year after the stroke (75.2 at 3 months; 75.4 at 1 year).

[a]Caregiver burden score measures general strain (items 1 to 8), isolation (items 9 to 11), disappointment (items 12 to 16), emotional involvement (items 17 to 19), and environment (items 20 to 22), which together encompass important domains of the caregiving burden. These items are all scored from 1 to 4 (not at all, seldom, sometimes, often).
[b]HADS comprises 14 questions, of which half make up the anxiety subscale and half the depression subscale. Response options include “not at all,” “occasionally,” “quite often,” and “very often,” which are scored 0, 1, 2, or 3. A higher number indicates a more negative response, and a score of >8 is considered indicative of need for further assessment.

B.1.3.4.4 *Economic burden*

Owing to the severity and clinical burden associated with CV events, resource use, especially hospitalisation, is high in patients with ASCVD (40, 47-50). Cardiovascular disease places a substantial burden on the healthcare system in the UK, with healthcare costs amounting to £9 billion per year (6). Over 100,000 hospital admissions and 200,000 hospital visits per year are due to heart attacks alone. Around 60% of ASCVD patients are admitted into hospital for their first acute event (8). In addition to healthcare costs, the economic impact of CVD in the UK is estimated to total £19 billion per year, due to premature death, disability and informal costs (6).

In a retrospective cohort study assessing resource use for 24,093 patients who had experienced a CV event in the UK between January 2006 and March 2012, the mean length of hospitalisation following the first CV event was shortest following unstable angina (4.5 days), and was longest following ischaemic stroke (IS; 22.5 days) (40). Following a second event, the mean length of hospitalisation was longer (4.9 days following unstable angina and 26.7 days following IS). In addition, resource use was higher following a second event compared with that following a first event in both the short- and long-term.

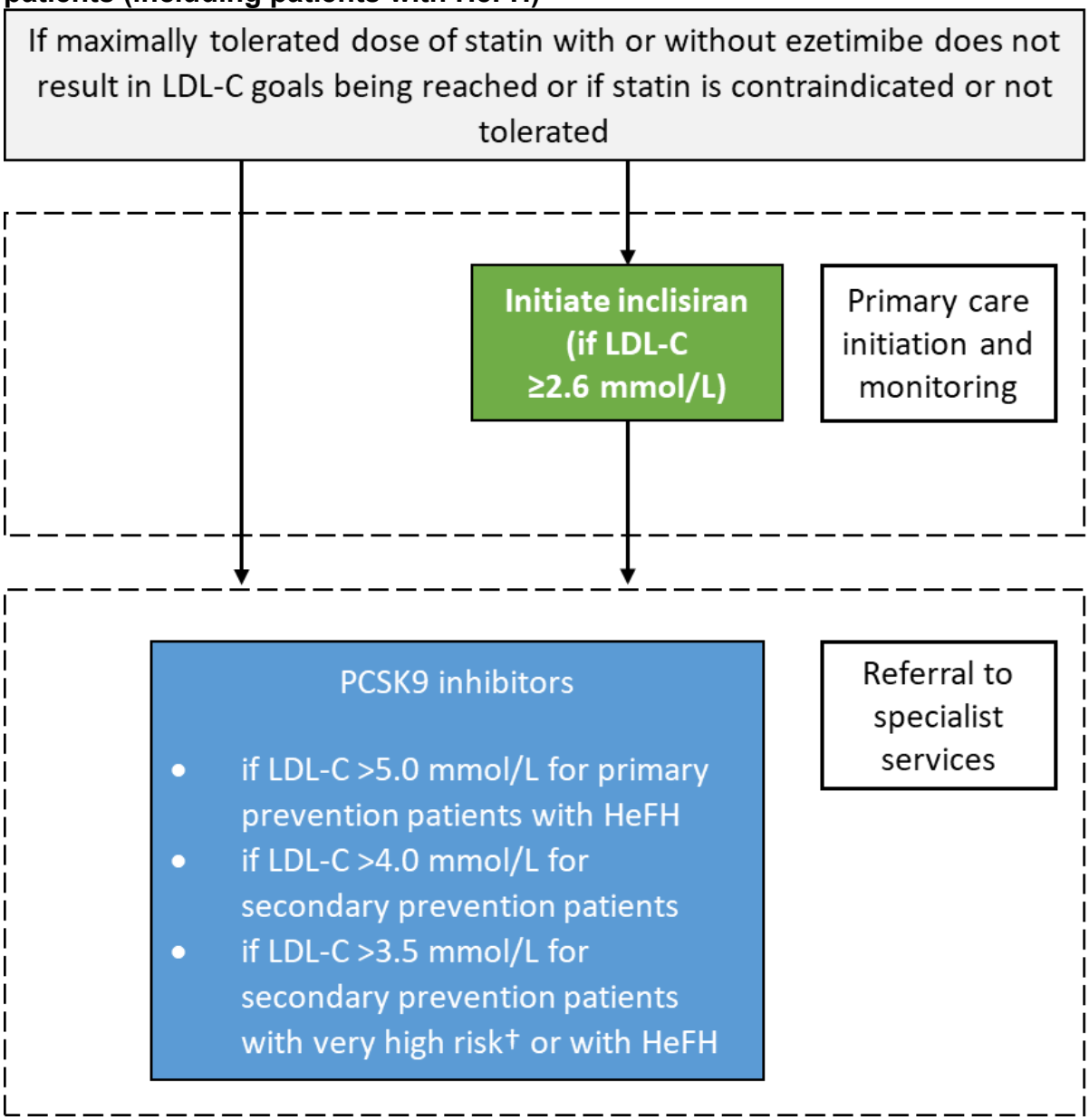
In the same study, total costs were substantially higher in the first 6 months following a first CV event (incremental cost, £3,504.01), than in patients without a CV event (40). There was a decrease in costs from Month 1–6 to Month 7–36, but costs remained higher than in the 12 months prior to a first CV event (incremental cost, £361.11). Following a second CV event, total costs were higher in Month 1–6 (£3,967.74) and Month 7–36 (£1,017.68), compared with the 12 month period before the first event, and were higher than the costs in the corresponding periods following the first event. When broken down by CV event, the cost following a second event was consistently higher than that following a first event, with the exception of the cost of revascularisation, which was associated with lower costs in Months 1–6 following a second event.

B.1.3.5 Clinical pathway of care

The following description of the pathway of care is based on the NHS Accelerated Access Collaborative summary of national guidance for lipid management (51), National Institute for Health and Care Excellence (NICE) clinical guidelines CG181 (9), CG71 (52), and technology appraisal guidance TA385 (53), TA393 (11) and TA394 (12).

The clinical pathway of care (including the proposed positioning of inclisiran) for secondary prevention of ASCVD (including patients with HeFH) and PPER patients (including patients with HeFH) is presented in Figure 3.

Figure 3: Proposed positioning of inclisiran in the clinical pathway of care for secondary prevention of ASCVD (including patients with HeFH) and PPER patients (including patients with HeFH)



Adapted from NHS Accelerate Access Collaborative summary of national guidance (51)
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Hypercholesterolaemia is treated with lifestyle modifications (including dietary changes, exercise and smoking cessation) and lipid modification therapies, primarily high intensity statins.

If desired reductions in LDL-C levels are not achieved with statins, additional options for treatment include the cholesterol absorption inhibitor ezetimibe, then monoclonal

antibodies targeted to proprotein convertase subtilisin/kexin type 9 (PCSK9) for higher risk patients above specific LDL-C thresholds i.e. 5 mmol/L for HeFH patients without CVD, 4 mmol/L for non-FH patients with CVD, and 3.5 mmol/L for very high risk of CVD[c] non-FH patients and for HeFH patients with CVD.

The LDL-C threshold deemed most clinically plausible and cost-effective for this population is 2.6 mmol/L. The reasons for this are many and have been outlined below. Most importantly, however, clinical experts in the UK have recommended a 2.6 mmol/L threshold as it is the level they see patients gaining the maximum benefit based on clinical trial outcomes to date.

Studies from the ORION clinical trial programme used LDL-C thresholds at a level of ≥1.8 mmol/L (ASCVD patients in ORION 10, and 11) and ≥2.6 mmol/L (HeFH in ORION 9; PPER in ORION 11) to define the patient population. The population within these trials achieved statistically significant reductions in their LDL-C levels, providing clinical evidence to support ≥2.6 mmol/L as an appropriate threshold for inclisiran usage in both primary and secondary prevention cohorts (17, 54).

Further substantiation is provided by the ODYSSEY OUTCOMES trial, a clinical trial with alirocumab assessing clinical outcomes after acute coronary syndrome. The study showed that the absolute benefit with respect to the composite primary endpoint (death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalisation) was more pronounced in patients who had a baseline LDL-C level of ≥2.6 mmol/L (18). Using patient level data from this trial, a cost-effectiveness model was developed to estimate costs and outcomes over a lifetime horizon. The results showed that in patients with a recent acute coronary syndrome on optimal statin therapy, alirocumab improved cardiovascular outcomes at costs considered intermediate value, with good value in patients with baseline ≥2.6 mmol/L (55).

In addition, a meta-analysis of 34 randomised clinical trials including 270,288 participants assessed the association between baseline LDL-C level and both all-

[c] defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease)

cause and cardiovascular mortality after LDL-C lowering treatment. This study showed that the greatest benefit from LDL-C lowering therapies occurred in patients with a baseline LDL-C level of ≥2.6 mmol/L or greater, as more intensive LDL-C lowering therapy was associated with a progressive reduction in both all-cause and cardiovascular mortality with higher baseline LDL-C levels. This relationship was not present in patients with a baseline level of less than 2.6 mmol/L (56).

More recently, the DA VINCI study, an EU-wide cross-sectional observational study on lipid lowering therapy use in secondary and primary care, aimed to provide data on the implementation of European guideline recommendations for lipid-lowering therapies across different settings and populations. The 2019 ESC/EAS guidelines outline LDL-C targets of <2.6 mmol/L, <1.8 mmol/L and <1.4 mmol/L in moderate, high risk and very high-risk patients, respectively. Of the 5888 patients enrolled in the study, only 33% achieved their risk-based goal as defined in the 2019 guidelines (57). This study therefore demonstrated that only one-third of patients achieved the ESC/EAS 2019 goals, despite high-intensity statin treatment. This highlights the need for intervention in addition to high-intensity statin amongst patients with an LDL-C above a threshold of 2.6 mmol/L.

The above evidence is supported by clinical opinion, with expert input validating the threshold of ≥2.6 mmol/L. Expert opinion also highlighted that patients with a baseline LDL-C level of ≥2.6 mmol/L could expect around a 50% lowering of LDL-C based on ORION clinical trial data. As this would be associated with an average absolute reduction in LDL-C of 1.3–1.4 mmol/L, this would likely translate to a 30% reduction in event risk based on the accepted risk reduction seen in the CTT analyses (5).

Inclisiran will be used in combination with statins and/or other lipid lowering therapies in patients unable to reach target LDL-C goals when already receiving maximum tolerated dose of a statin. Inclisiran can also be initiated as a monotherapy or in combination with other lipid lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated.

As described in Section B.1.1, the proposed population (patients with LDL-C ≥2.6 mmol/L) is narrower than the marketing authorisation but is the population to reflect the available clinical evidence and in whom the greatest clinical benefit is expected.

B.1.3.5.1 *Lifestyle modification for primary and secondary prevention of CVD*

People at high risk of or with CVD are advised to eat a diet in which total fat intake is ≤30% of total energy intake, saturated fats are ≤7% of total energy intake, intake of dietary cholesterol is less than 300 mg/day, and where possible, saturated fats are replaced by mono-unsaturated and polyunsaturated fats (58).

They are also advised to undertake at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity (or a combination of both) per week (58).

B.1.3.5.2 *Statins for primary and secondary prevention of CVD*

When a decision is made to use statins, NICE guidelines recommend that high intensity statins are used (9, 52). A high intensity statin is defined as a dose which achieves a >40% reduction in LDL-C levels.

In primary prevention, people with a >10% 10-year risk of developing CVD (according to QRISK2 (31)) are recommended atorvastatin 20 mg as an initial treatment. In secondary prevention, people with CVD should be initiated with a statin treatment of atorvastatin 80 mg. For both primary and secondary prevention, response to treatment should be assessed 3 months after initiation. If a >40% reduction in non-HDL-C is not achieved, clinicians may consider increasing the dose if started on less than atorvastatin 80 mg initially and if the person is judged to be at higher risk owing to comorbidities, risk score or based on clinical judgement.

In adults with FH, guidelines recommend a high-intensity statin with the lowest acquisition cost as the initial treatment (52). In these patients, the target is a >50% reduction in LDL-C from the baseline measurement. The dose of statin should be increased to the maximum licensed or tolerated dose to achieve this.

B.1.3.5.3 *Ezetimibe for treating primary hypercholesterolaemia*

Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who have started statin therapy when serum total or LDL-C concentrations are not appropriately controlled[d], and a change to an alternative statin is being considered (53).

Ezetimibe is also recommended as a monotherapy in this patient population if initial statin therapy is contraindicated, or if statin therapy cannot be tolerated[e].

B.1.3.5.4 *PCSK9 inhibitors for treating primary hypercholesterolaemia and mixed dyslipidaemia*

Current NICE guidance recommends use of PCSK9 inhibitors alirocumab and evolocumab when LDL-C levels are persistently above the thresholds specified in Table 4 despite receiving maximal tolerated lipid-lowering therapy (11, 12).

Table 4: LDL-C concentrations above which alirocumab and evolocumab are recommended by NICE

	Without CVD	With CVD	
		High risk of CVD†	Very high risk of CVD‡
Primary non-FH or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l
Primary HeFH	Recommended only if LDL-C concentration is persistently above 5.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l	

†High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.
‡Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).
Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol.

[d] Appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease in the relevant populations

[e] Intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy

B.1.3.5.5 *Apheresis*

Apheresis is generally prescribed for homozygous familial hypercholesterolaemia, (which is not part of the indication for inclisiran) and is used very infrequently 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” (12).

B.1.3.6 Unmet need

B.1.3.6.1 *ASCVD remains a major cause of morbidity, mortality and economic burden*

Cardiovascular disease is a leading cause of death globally, accounting for approximately 18 million deaths per year (31% of overall deaths), a figure that is expected to increase (35). Elevated LDL-C is a major cause of ASCVD which is a subset of CVD and accounts for approximately 4 in 5 of all CVD deaths (35). Preventing premature mortality due to CVD remains a key priority (33).

In addition, non-fatal major CV events can lead to serious long-term consequences such as functional disability, impaired HRQoL, and an increased risk of subsequent CV events. In a retrospective analysis using the Clinical Practice Research Datalink (CPRD) that was used to inform event rates in the economic model (Section B.3.3.2.1), patients with ASCVD were found to have an [redacted] annual risk of further CV events (Appendix L).

Cardiovascular disease also represents a significant economic burden. By 2030 the total global cost of CVD is set to rise from approximately $863 billion in 2010 to more than $1 trillion (59).

B.1.3.6.2 *Statins do not provide adequate reductions in LDL-C*

There are two key reasons why patients do not achieve LDL-C goals with statins:

1. Current maximal dose therapy has insufficient efficacy

Despite significant progress over the last 30 years, an unmet need remains for medicines that reduce LDL-C beyond the reductions obtained with statins. Even well-managed ASCVD patients – given lifestyle guidance, escalated intensity of statins, then given adjunctive ezetimibe – may still not reach guideline-recommended LDL-C levels. A prospective cohort study of 165,411 primary care patients in the UK found that 84,609 (51%) did not achieve an optimal LDL-C response (defined as ≥40% reduction from baseline) within 24 months (10). In an analysis of real world data in the UK, only 16% of patients achieved LDL-C <2 mmol/L within 12 months of secondary care intervention (60).

2. Many patients fail to adequately comply with therapy

The challenge of adherence is a significant unmet need for high-risk (ASCVD or FH) patients as it leads to suboptimal reductions in LDL-C levels and, as a result, increases the risk of CVD morbidity and mortality.

In a study of adherence to coronary heart disease secondary prevention medicines (median number of individual daily doses = 6), 43.5% of patients were non-adherent to ≥1 medicine (61). Further published evidence has shown a significant increase in mortality and the incidence of CVD in less adherent patients (62).

B.1.3.6.3 *The addition of oral lipid-lowering therapies to statins does not provide adequate reductions in LDL-C*

For patients with elevated LDL-C levels despite treatment with statins, additional lipid-lowering therapies are required. NICE guidelines recommend that ezetimibe and other oral lipid-lowering therapies are additionally prescribed (53), but their potency is limited, with additive LDL-C reductions with ezetimibe in the order of 20% (63). Although existing treatment options adequately reduce LDL-C levels in most patients, for very-high risk individuals, the combination of a statin plus ezetimibe is unlikely to achieve sufficient LDL-C lowering (57). Such patients have a substantial unmet medical need for a further therapy that can be added to a statin with or without ezetimibe.

B.1.3.6.4 *PCSK9 mAb inhibitors*

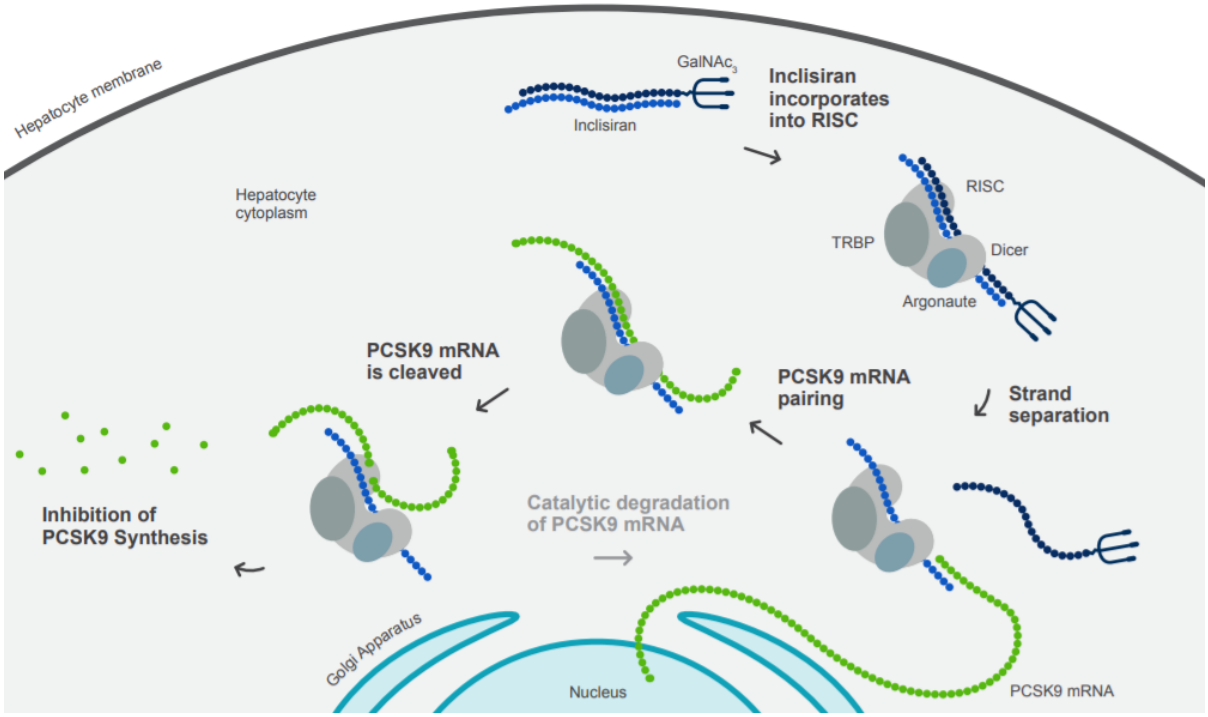
Monoclonal antibodies against PCSK9 have been shown to effectively reduce LDL-C levels (13, 14). However, they require subcutaneous administration every 2 to 4 weeks. Patients or caregivers may administer these therapies, but they need to be trained to do so. If they do not feel comfortable doing this, the patient needs to attend fortnightly or monthly appointments to receive medication, which is inconvenient for patients and has resource implications for clinical practice.

The availability of a therapy that provides a sustained and effective reduction in LDL-C levels with a twice-yearly dosing regimen is expected to be preferable for patients, with the potential to improve adherence and to minimise the burden on healthcare services.

B.1.3.7 Inclisiran

Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA) conjugated with triantennary N-acetylgalactosamine (GalNAc) carbohydrate to facilitate specific and rapid uptake by hepatocytes. Following cell entry, the antisense strand of RNA incorporates into the RNA-induced silencing complex (RISC), acting as a template for the RISC to recognise and degrade the messenger RNA (mRNA) encoding the PCSK9 protein. By inhibiting the production of PCSK9, LDL receptors are spared from degradation, increasing uptake of LDL-C into the liver and reducing circulating LDL-C levels (Figure 4).

Figure 4: Mechanism of action of inclisiran



Abbreviations: GalNAc, N-Acetylgalactosamine; mRNA, messenger RNA; PCSK9, proprotein convertase subtilisin/kexin type 9; RISC, RNA-induced silencing complex; TRBP, transactivation response RNA binding protein.

Inclisiran is anticipated to be licensed for 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 (16).

Inclisiran will be administered twice-yearly by a healthcare professional (after initial dosing and at 3 months), compared with PCSK9 inhibitors which are administered on a fortnightly or monthly basis either by the patient or a trained individual. The combination of inclisiran's sustained efficacy and twice-a-year maintenance dosing means that the treatment offers the potential to help patients reach their LDL-C goals with minimal administration requirements for the healthcare system. This may lead to

better adherence in the management of hypercholesterolaemia, with minimal burden on the healthcare system.

B.1.4 Equality considerations

Cardiovascular disease is one of the health conditions most strongly associated with health inequalities, with unwarranted variation in the uptake of innovative products that are delivered exclusively in secondary care. The inclisiran population health collaboration with NHS England (under which inclisiran will be delivered in primary care) is expected to improve equality in care provision. Full details are available in Section B.2.12.2.

B.2 Clinical effectiveness

The clinical development programme for inclisiran includes three randomised, double-blind, placebo-controlled, Phase 3 trials

- ORION-9, -10 and -11 provide more than 3,000 patient-years of data on inclisiran's safety and LDL-C lowering effect after 18 months of treatment. They assessed the efficacy and safety of inclisiran (284 mg) compared with placebo on top of a maximally tolerated dose of statin, for the treatment of:
  - **ORION-9:** Patients with HeFH and elevated LDL-C
  - **ORION-10:** Patients with ASCVD and elevated LDL-C
  - **ORION-11:** Patients with ASCVD or ASCVD-RE (termed PPER within this submission) and elevated LDL-C
- All three trials shared identical primary and secondary endpoints, and participants are eligible for inclusion in the Phase 3 extension study, ORION-8
- Key patient demographics, disease characteristics, and lipid lowering therapy usage at baseline were generally well-balanced between arms within trials

All trials met their co-primary endpoints, demonstrating that after two starter doses (at Month 0 and Month 3), twice-yearly subcutaneous dosing with inclisiran resulted in sustained LDL-C reductions vs placebo

- Treatment with inclisiran resulted in a ≥50% placebo-adjusted reduction in LDL-C at Day 510, and a ≥44% time-adjusted reduction in LDL-C after Day 90 and up to Day 540
- LDL-C targets were met by 77% (ORION-9), 94% (ORION-10) and 92% (ORION-11) of patients. These results would be expected to translate into a clinically meaningful reduction in risk of CV events

Network meta-analysis suggests that inclisiran is comparable to alirocumab and evolocumab at improving cholesterol levels, across various hypercholesteremia patient populations

- Both alirocumab and evolocumab convey numerically but not statistically significant advantages over inclisiran in percentage change in LDL-C at 24

weeks across the patient populations in which NMA was feasible (ASCVD and PPER, both with maximally tolerated dose [MTD] statin and with statin intolerance; HeFH, with MTD statin), which suggests that inclisiran provides outcomes expected to be comparable to alirocumab and evolocumab

- The addition of inclisiran to current standard-of-care for patients with ASCVD, PPER and HeFH generally results in statistically significant improvements in LDL-C, HDL-C, and comparable tolerability to standard-of-care alone

Treatment with inclisiran over 18 months demonstrated a safety profile comparable to placebo (except for injection site reactions)

- More inclisiran-treated patients reported TEAEs at the injection site than placebo-treated patients (8.2% vs 1.8% experienced TEAEs at the injection site, respectively, across the studies; 0.2% vs 0.0% discontinued due to these TEAEs, respectively)
- However, all TEAEs at the injection site were localised, predominantly mild or occasionally moderate, transient (i.e. resolving prior to the next dose), and resolved without sequelae
- There were no differences in hepatic, renal, and diabetic safety parameters compared with placebo, and the safety profile of inclisiran was consistent across all subgroups

The inclisiran population health collaboration with NHS England is expected to improve equality in care provision, representing a benefit that cannot be captured in the QALY calculation

- Cardiovascular disease is one of the health conditions most strongly associated with health inequalities, driving the life expectancy gap as the greatest cause of premature mortality in areas of deprivation, with 40% of all amenable deaths in CVD in the three most deprived deciles (64).
- Unwarranted variation in the uptake of innovative products that are delivered exclusively in secondary care is well established. In the cardiovascular field, Novartis has recent data demonstrating that uptake of sacubitril valsartan ranges from as [redacted] of the NICE-eligible patient population across localities within England.

- Under the framework of the inclisiran population health collaboration with NHS England, inclisiran will potentially be delivered [redacted] within primary care using proactive care delivery models, making full use of the recently established Primary Care Networks (PCNs) in order to reduce the burden on outpatient and secondary care departments.
- Significant activity is underway with the Accelerated Access Collaborative to support delivery of the population health model and appropriate uptake of inclisiran, which is expected to represent a step-change in the management of patients [redacted]

B.2.1 Identification and selection of relevant studies

A systematic literature review was conducted to identify relevant clinical effectiveness studies. Studies identified are listed in Table 5. Appendix D contains the full details of the process and methods used in the clinical SLR.

Table 5: RCTs identified by the clinical effectiveness SLR

Inclisiran	Alirocumab	Evolocumab	Ezetimibe
• **ORION-9 (54)** • **ORION-10 (17)** • **ORION-11 (17)** • **ORION-1 (65)†**	• **ODYSSEY ALTERNATIVE (66)** • **ODYSSEY CHOICE I (67)** • **ODYSSEY CHOICE II (68)** • **ODYSSEY COMBO I (69)** • **ODYSSEY COMBO II (70)** • **ODYSSEY EAST (71)** • **ODYSSEY FH I (72)** • **ODYSSEY FH II (72)** • **ODYSSEY HIGH FH (73)** • ODYSSEY JAPAN (74, 75) • **ODYSSEY KT (76)** • **ODYSSEY LONG TERM (77)** • **ODYSSEY NIPPON (78)** • ODYSSEY OPTIONS I (79) • ODYSSEY OPTIONS II (80) • **ODYSSEY OUTCOMES (18)**	• DESCARTES (84) • **FOURIER (85)** • **GAUSS-2 (86)** • GAUSS-3 (87) • **GAUSS-4 (88)** • **LAPLACE-2 (89)** • **RUTHERFORD-2 (90)** • YUKAWA-2 (91) • GAUSS (92) • **LAPLACE-TIMI 57 (93)** • RUTHERFORD (94) • YUKAWA (95)	• EASEGO (96) • Luo 2016 (97) • Nakamura 2012 (98) • TACO (99)

Inclisiran	Alirocumab	Evolocumab	Ezetimibe
	• **NCT01288443 (Mckenney 2012) (81)** • **NCT01266876 (Stein 2012) (82)** • NCT01812707 (Teramoto 2016) (83)		

Trials marked in bold are included in the NMA (full trial populations or subgroups).
†ORION-1 is a Phase 2 study so does not inform the clinical or cost-effectiveness evidence provided in this submission.

B.2.2 List of relevant clinical effectiveness evidence

Three Phase 3 trials (ORION-9, -10 and -11) inform the clinical evidence base and economic model for inclisiran in hypercholesterolaemia and mixed dyslipidaemia. An overview of these trials is provided in Table 6–Table 8.

Table 6: Clinical effectiveness evidence (ORION-9)

Study	ORION-9 (NCT03397121) Raal et al, 2020 (54)				
Study design	Randomised, double-blind, placebo-controlled, Phase 3 trial				
Population	Patients with HeFH and elevated LCL-C (N=482)				
Intervention(s)	Inclisiran (284 mg)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	ORION-9 is used in the model as it is a pivotal RCT				
Reported outcomes specified in the decision problem	• Plasma lipid and lipoprotein levels, including **LDL-cholesterol**†, non-HDL cholesterol, apolipoprotein B and lipoprotein-a • Fatal and non-fatal cardiovascular events • Mortality • Adverse effects of treatment				
All other reported outcomes	NA				

†Marked bold as this outcome from the trial is used in the economic model.
Abbreviations: HDL, high density lipoprotein; HeFH, heterozygous familial hypercholesterolaemia; LCL-C, low density lipoprotein cholesterol; NA, not applicable; RCT, randomised controlled trial.

Table 7: Clinical effectiveness evidence (ORION-10)

Study	ORION-10 (NCT03399370) Ray et al, 2020 (17)				
Study design	Randomised, double-blind, placebo-controlled, Phase 3 trial				
Population	Patients with ASCVD and elevated LDL-C (N=1,561)				
Intervention(s)	Inclisiran (284 mg)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	ORION-10 is used in the model as it is a pivotal RCT				
Reported outcomes specified in the decision problem	• Plasma lipid and lipoprotein levels, including **LDL-cholesterol**†, non-HDL cholesterol, apolipoprotein B and lipoprotein-a • Fatal and non-fatal cardiovascular events • Mortality • Adverse effects of treatment				
All other reported outcomes	• Pharmacokinetics				

†Marked bold as this outcome from the trial is used in the economic model.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL, high density lipoprotein; LDL-C, low density lipoprotein cholesterol; RCT, randomised controlled trial.

Table 8: Clinical effectiveness evidence (ORION-11)

Study	ORION-11 (NCT03400800) Ray et al, 2020 (17)				
Study design	Randomised, double-blind, placebo-controlled, Phase 3 trial				
Population	Patients with ASCVD or ASCVD risk-equivalents† and elevated LDL-C (N=1,617)				
Intervention(s)	Inclisiran (284 mg)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	ORION-11 is used in the model as it is a pivotal RCT				
Reported outcomes specified in the decision problem	• Plasma lipid and lipoprotein levels, including **LDL-cholesterol**¶, non-HDL cholesterol, apolipoprotein B and lipoprotein-a • Fatal and non-fatal cardiovascular events • Mortality • Adverse effects of treatment				
All other reported outcomes	NA				

†'ASCVD risk-equivalent' is the term used in the study publication. This term is synonymous with the term 'primary prevention with elevated risk (PPER)' used throughout this dossier; ¶Marked bold as this outcome from the trial is used in the economic model.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL, high density lipoprotein LDL-C, low density lipoprotein cholesterol; NA, not applicable; RCT, randomised controlled trial.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The clinical development programme for inclisiran includes three randomised, double-blind, placebo-controlled, Phase 3 trials (ORION-9, -10 and -11) providing more than 3,000 patient-years of data on inclisiran's safety and LDL-C lowering effect after 18 months of treatment. They assessed the efficacy and safety of inclisiran (284 mg) compared with placebo on top of a maximally tolerated dose of statin, for the treatment of:

- **ORION-9:** Patients with HeFH and elevated LDL-C
- **ORION-10:** Patients with ASCVD and elevated LDL-C

- **ORION-11:** Patients with ASCVD or atherosclerotic cardiovascular disease risk-equivalent (ASCVD-RE; termed PPER within this submission) and elevated LDL-C.

The trial protocols for ORION-10 and -11 were identical, with the exception of broader inclusion criteria in ORION-11 which also includes patients with ASCVD-RE (termed PPER within this submission). The trials provide combined safety and tolerability data in over 3,000 individuals with ASCVD or ASCVD-RE (termed PPER within this submission). ORION-9 assessed safety and efficacy in a distinct group of patients, but the design and objectives of the study were generally the same as ORION-10 and -11. All three trials shared identical primary and secondary endpoints, and participants are eligible for inclusion in the Phase 3 extension study, ORION-8.

Given the significant overlap in the methodology of the ORION Phase 3 trials, a combined summary is presented in this section and in Section B.2.4.

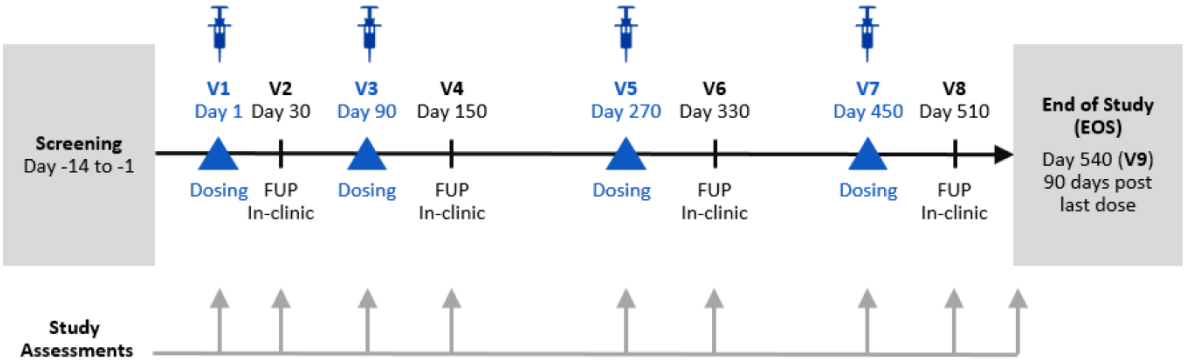
B.2.3.1 Trial design

Patients were randomised 1:1 to receive inclisiran or placebo. Treatment allocation was stratified in block sizes of 4 by:

- current use of statins or other lipid lowering therapies (all three trials)
- country (ORION-9 and 11 only, as ORION-10 was conducted in the United States).

The studies lasted for 18 months, with treatments administered on Day 1, Day 90, Day 270, and Day 450 (Figure 5).

Figure 5: Schematic of ORION-9, 10 and 11 designs



Abbreviations: FUP, follow-up; V, visit.

B.2.3.2 Outcomes used in the economic model/specified in the scope

All efficacy parameters in the studies were laboratory assessments. Parameters assessed included: total cholesterol (TC), triglycerides, LDL-C, HDL-C, non-HDL-C, very low density lipoprotein cholesterol (VLDL-C), apolipoprotein B (Apo-B), lipoprotein-a, and PCSK9.

It is noted that NICE guideline CG181 recommends the use of non-HDL-C rather than LDL-C to direct diagnosis, treatment initiation and ongoing management, as LDL-C requires a calculation using a fasting sample and for triglycerides to be less than 4.5 mmol/l, whereas the measurement of non-HDL-C does not (see Section B.1.3.1) (9). However, in the ORION trial programme (in which LDL-C was the primary outcome based on regulatory requirements), patients were in a fasted state for all efficacy laboratory assessments. Furthermore, NICE recommendations for comparators for this appraisal include LDL-C thresholds (9, 11, 12, 53). Therefore, LDL-C is used in this submission rather than non-HDL-C.

B.2.3.2.1 *Co-primary endpoints (all trials)*

- Percentage change in LDL-C from baseline to Day 510.
- Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. *This is the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540, reflecting effects on LDL-C levels at a steady state akin to a more chronic dosing regimen. The Day 90 dose is the start of the 6-monthly dosing regimen.*

B.2.3.2.2 *Key secondary endpoints (all trials)*

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

B.2.3.2.3 *Other secondary endpoints (all trials)*

- Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540.
- Absolute change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B and non-HDL-C.
- Individual responsiveness defined as the number of patients reaching on-treatment LDL-C levels of <25 mg/dl (0.65 mmol/l), <50 mg/dl (1.30 mmol/l), <70 mg/dl (1.81 mmol/l), and <100 mg/dl (2.59 mmol/l) at Day 510.
- Proportion of patients in each group with greater or equal to 50% LDL-C reduction from baseline.
- Proportion of patients in each group who attain global lipid targets for their level of ASCVD risk.
- Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540.
- Maximum percentage change in LDL-C. This is calculated by finding the maximum individual LDL-C reduction at any post-baseline visit for each individual patient. This value was used to compare against each patient's baseline value and used to calculate the percent change from baseline to the lowest LDL-C value.

B.2.3.2.4 *Exploratory endpoints*

ORION-9

- Major adverse cardiac event (MACE) defined as the composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic or haemorrhagic) using a broad basket of MedDRA terms to identify events.
- Proportion of patients in each group with any LDL-C reduction from baseline at any visit (responders).
- Response of LDL-C reduction by underlying causal mutations of HeFH.

ORION-10

- MACE defined as the composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic or haemorrhagic) using a pre-defined MedDRA search to identify events.

ORION-11

- MACE defined as the composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic or haemorrhagic) using a pre-defined MedDRA search to identify events.
- Proportion of patients in each group with any LDL-C reduction from baseline at any visit (responders).

B.2.3.3 Eligibility criteria

Key inclusion and exclusion criteria are listed in Table 9. Differences in inclusion criteria for disease history and serum LDL-C reflect the indications under assessment in each trial.

Table 9: Key inclusion and exclusion criteria

ORION-9	ORION-10	ORION-11
Key inclusion criteria		
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	History of ASCVD (CHD, CVD or PAD)	History of ASCVD (CHD, CVD or PAD) or ASCVD-RE (T2D, FH, and including patients whose 10-year risk of a CV event assessed by Framingham Risk Score (32) or equivalent has a target LDL-C of <2.6 mmol/l [100 mg/dl])
Serum LDL-C ≥2.6 mmol/l (100 mg/dl)	Serum LDL-C ≥1.8 mmol/l (70 mg/dl)	Serum LDL-C ≥1.8 mmol/L (70 mg/dl) for ASCVD patients or ≥2.6 mmol/L (100 mg/dl) for ASCVD risk-equivalent patients at screening
Patients on statins should have been receiving a maximally tolerated dose. Maximum tolerated dose was defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events		
Patients not receiving statin must have had documented evidence of intolerance to all doses of at least two different statins		
Key exclusion criteria		
An underlying known disease, or surgical, physical, or medical condition that, in the opinion of the investigator (or delegate) may have interfered with interpretation of the clinical study results		
Previous or current treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9		
Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever was longer		
Planned use of other investigational products or devices during the course of the study		

ORION-9	ORION-10	ORION-11
NYHA class IV heart failure or last known left ventricular ejection fraction <25%		
Cardiac arrhythmia within 3 months prior to randomisation that was not controlled by medication or via ablation		
MACE within 3 months prior to randomisation		
Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomisation despite anti-hypertensive therapy		
Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in ALT, AST, >3x ULN, or total bilirubin >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart		
Severe concomitant non-cardiovascular disease that carried the risk of reducing life expectancy to less than 2 years		

Abbreviations: ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; ASCVD-RE, atherosclerotic cardiovascular disease risk-equivalents; AST, aspartate aminotransferase; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac event; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; T2D, type 2 diabetes; ULN, upper limit of normal.

B.2.3.3.1 *Definition of ASCVD risk-equivalent population in ORION-11*

In ORION-11, individuals were categorised as having ASCVD-RE (termed PPER within this submission) factors if they had LDL-C levels ≥2.6 mmol/L, plus any of the following:

- type 2 diabetes (65.0% of patients in ORION-11)
- familial hypercholesterolaemia (14.8%)
- 10-year ASCVD risk of ≥20% according to the Framingham risk score (32) or equivalent (20.2%).

‘ASCVD-RE’ is the term used in the study publication. This term is synonymous with the term ‘primary prevention patients with elevated risk (PPER)’ used throughout this dossier.

B.2.3.4 Settings and locations where the data were collected

Table 10 details the number of study centres and countries included in each trial.

Table 10: Number of study centres and countries for each trial

Trial	Number of centres	Number of countries	Number of UK sites and patients
ORION-9	47	8	0
ORION-10	146	1†	0
ORION-11	72	8	23 sites 462 patients

†ORION-10 took place in the US only

Across the three trials, patients were recruited in Canada, Czech Republic, Denmark, Germany, Hungary, Netherlands, Poland, South Africa, Spain, Sweden, UK, and USA.

B.2.3.5 Trial drugs and concomitant medications

The intervention was inclisiran (284 mg). The comparator was placebo (0.9% sodium chloride in water) administered in the same 1.5 ml volume and packaged in the same container to maintain blinding. Both inclisiran and placebo were administered subcutaneously. The dosing schedule is shown in Figure 5.

B.2.3.5.1 *Prior and concomitant medications*

Patients on statins were to be receiving a maximally tolerated dose (defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events). Patients on lipid-lowering therapies (such as a statin and/or ezetimibe) were to have been on a stable dose for ≥30 days before screening and were to remain on the dose that they had received during participation in the original protocol unless clinically indicated.

Permitted and prohibited concomitant medications are detailed in Table 11.

Table 11: Permitted and prohibited concomitant medications in ORION-9, 10 and 11

Permitted	Prohibited
• Hormone replacement therapy • Lipid-lowering medications; patients already on stable (≥30 days before screening) lipid-lowering medications (such as statins and/or ezetimibe) were to remain on the dose that they had received during participation in the original protocol unless clinically indicated • Prescription medications prescribed to treat pre-existing medical conditions such as diabetes and hypertension • Prescription or non-prescription medications, when necessary to treat an AE, and at the discretion of the investigator	• Medications prescribed to lower LDL-C (e.g. statins, ezetimibe, lomitapide, mipomersen, niacin, colesevelam, bile acid absorption inhibitors, monoclonal antibodies directed towards PCSK9) • Any medication taken for the purpose of lipid lowering, including over-the-counter or herbal therapies

Abbreviations: AE, adverse event; LDL-C, low density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

B.2.3.6 Baseline characteristics

Key patient demographics, disease characteristics, and lipid lowering therapy usage at baseline are presented in Table 12. These were generally well-balanced between arms within trials.

Differences between trials reflect the indications under review in each study. For example, mean age was lower in ORION-9 as one of the defining features of HeFH is early-onset ASCVD.

Table 12: Characteristics of participants in the studies across treatment groups (ITT)

	ORION-9		ORION-10		ORION-11	
	Placebo (N=240)	Inclisiran (N=242)	Placebo (N=780)	Inclisiran (N=781)	Placebo (N=807)	Inclisiran (N=810)
Age (years)						
Mean ± SD	55.0±11.81	54.4±12.48	65.7±8.89	66.4±8.90	64.8±8.68	64.8±8.29
Median (IQR)	56 (47–63)	56 (46–64)	66 (59–72)	67 (61–72)	65 (59–71)	66 (60–70)
Sex						
Male, n (%)	115 (47.9)	112 (46.3)	548 (70.3)	535 (68.5)	581 (72.0)	579 (71.5)
Race						
White, n (%)	227 (94.6)	226 (93.4)	685 (87.8)	653 (83.6)	796 (98.6)	791 (97.7)
Cardiovascular risk factors, n (%)						
ASCVD	73 (30.4)	59 (24.4)	780 (100)	781 (100)	702 (87.0)	712 (87.9)
ASCVD risk-equivalent[†]	167 (69.6)	183 (75.6)	0 (0)	0 (0)	105 (13.0)	98 (12.1)
Lipid lowering therapy, n (%)						
Any	226 (94.2)	229 (94.6)	730 (93.6)	748 (95.8)	781 (96.8)	784 (96.8)

	ORION-9		ORION-10		ORION-11	
	Placebo (N=240)	**Inclisiran (N=242)**	**Placebo (N=780)**	**Inclisiran (N=781)**	**Placebo (N=807)**	**Inclisiran (N=810)**
Statin	217 (90.4)	219 (90.5)	692 (88.7)	701 (89.8)	766 (94.9)	766 (94.6)
High-intensity statin	171 (71.2)	185 (76.4)	537 (68.8)	525 (67.2)	631 (78.2)	640 (79.0)
Ezetimibe	120 (50.0)	135 (55.8)	74 (9.5)	80 (10.2)	62 (7.7)	52 (6.3)
Cholesterol, mmol/l‡						
Total	6.0	5.9	4.7	4.7	4.7	4.8
LDL	4.0	3.9	2.7	2.7	2.7	2.8
HDL	1.3	1.3	1.2	1.2	1.3	1.3
Non-HDL	4.7	4.6	3.5	3.5	3.5	3.6
Other characteristics						
Apolipoprotein B ± SD, mg/dl	124.5±34.8	123.8±33.2	94.6±25.1	94.1±25.6	95.1±5.2	97.1±28.0
Median triglycerides (IQR), mg/dl	119 (85–166)	120 (82–167)	129 (96–182)	127 (92–181)	135 (102–185)	135 (99–181)
PCSK9 ± SD, µg/l	429.1±135.3	452.2±131.2	414.9±145.7	422.1±176.9	353±97.4	355±98.9

†Patients in this category had type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of 20% or greater as assessed by the Framingham Risk Score for Cardiovascular Disease (32) or equivalent.
‡These are converted from raw data (in mg/dl)
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL, high density lipoprotein; IQR, interquartile range; ITT, intention-to-treat; LDL, low density lipoprotein; LLT, lipid lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; SD, standard deviation.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

As per Section B.2.3, the descriptions provided in this section relate to all three trials, unless otherwise stated.

B.2.4.1 Hypothesis objective

The statistical hypotheses for the co-primary endpoints (Section B.2.3.2.1) were as follows:

- **Null hypothesis 1 (H01):** The difference (inclisiran minus placebo), between patients treated with inclisiran 284 mg and placebo in the least squares mean (LSM) percentage change in LDL-C from baseline at Day 510 equals zero
- **Null hypothesis 2 (H02):** The difference (inclisiran minus placebo), between patients treated with inclisiran 284 mg and placebo in the LSM time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 equals zero
- **Alternative hypothesis 1 (HA1):** The difference (inclisiran minus placebo), between patients treated with inclisiran 284 mg and placebo in the LSM percentage change in LDL-C from baseline at Day 510 is less than zero
- **Alternative hypothesis 2 (HA2):** The difference (inclisiran minus placebo), between patients treated with inclisiran 284 mg and placebo in the LSM time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 is less than zero

The family-wise type I error rate was controlled at a two-sided significance level of alpha=0.05 by using a nested testing procedure. The percentage change in LDL-C from baseline to Day 510 was tested first. If the null hypothesis was rejected at a two-sided significance level of alpha=0.05 and superiority of inclisiran over placebo was claimed, then the time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 was tested, also at a two-sided significance level of alpha=0.05.

B.2.4.2 Sample size and power calculation

Sample size calculations were performed with the assumption (based on observed results from a Phase II study (10)) that the difference in change from baseline between the active dose group and the placebo group for LDL-C would be no less than 30 mg/dl (0.8 mmol/l), with a standard deviation of 20 mg/dl (0.5 mmol/l).

Assuming a drop-out rate of 5%, the sample size would be approximately 380 (ORION-9) or 1,425 (ORION-10 and 11). This would provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared with the placebo group at one-sided significance level of 0.025.

In ORION-9, due to faster than expected enrolment, actual enrolment was 482 patients. This increased sample size contributed additional safety data and did not appreciably affect power calculations.

B.2.4.3 Analysis sets

The analysis sets listed below were defined in ORION-9, 10 and 11. For all analysis sets (except the safety set), treatment classification was based on the treatment assigned at randomisation.

- **Intention-to-treat (ITT):** all randomised patients. This was the primary efficacy analysis population.
- **Full analysis set (FAS):** all randomised patients who took any study medication and had at least one post-treatment lipid data measurement.
- **Modified intention-to-treat (mITT):** all randomised patients who received at least one dose of study drug and had both the baseline and the Day 510 follow-up LDL-C assessment.
- **Safety population:** all patients who received at least one dose of study drug. Treatment classification was based on the actual treatment received. This was the primary safety analysis population.

B.2.4.4 Data management and patient withdrawals

If missing data, defined as data not available from either scheduled (within the protocol defined visit window) or unscheduled visits, occurred for the primary or any key secondary efficacy endpoints (listed in Section B.2.4), then data were imputed as described in Sections B.2.4.4.1 and B.2.4.4.2.

B.2.4.4.1 *Percentage change in LDL-C from baseline to Day 510*

The primary method to impute missing data for the first co-primary efficacy endpoint was a multiple imputation washout model. The washout model was performed on actual values; change and percentage change values were calculated after the imputation. All retrieved data for patients who dropped out from study treatment were considered as non-missing data and utilised in all analyses.

In addition, sensitivity analyses using mixed-effect models for repeated measures (MMRM) without multiple imputation 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.

B.2.4.4.2 *Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540*

The control-based PMM described above was the primary method for imputing data for the second co-primary efficacy endpoint.

B.2.4.5 Statistical analysis of primary endpoints

The primary endpoints used a reflexive LDL-C approach: LDL-C was either calculated (based on the Friedewald formula), or measured directly using ultracentrifugation (if the calculated LDL-C was less than 40 mg/dl (1.0 mmol/l) or triglycerides were greater than 400 mg/dl (4.5 mmol/l), or calculated LDL-C was missing).

The co-primary endpoints were analysed as described in Sections B.2.4.5.1 and B.2.4.5.2.

B.2.4.5.1 *Percentage change in LDL-C from baseline to Day 510*

The primary analysis was conducted on the ITT population and based on an analysis of covariance (ANCOVA) model on the percentage change in LDL-C from baseline to Day 510 on each multiply imputed dataset (100 total). The model included fixed effects of treatment group and current use of statins or other lipid lowering therapy (LLT) at baseline (yes or no) and baseline LDL-C as a covariate.

Treatment effects from these 100 ANCOVA analyses were then combined using Rubin's Method (100) via the SAS PROC MIANALYZE procedure. The difference in the least squares means between treatment groups and corresponding two-sided 95% confidence interval (CI) was provided for hypothesis testing.

B.2.4.5.2 *Time-adjusted percentage change from baseline after Day 90 and up to Day 540*

The primary analysis was conducted on the ITT population and based on MMRM on the percentage change in LDL-C from baseline over all visits on each multiply imputed dataset (100 total). The model included fixed effects for treatment, visit, baseline value, interaction between treatment and visit, and current use of statins or other LLT. The Restricted Maximum Likelihood (REML) estimation approach was used with the covariance structure set as "Unstructured".

The time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 was calculated from the MMRM. Linear combinations of the estimated means after Day 90 and up to Day 540 were used to compare treatment effects.

Treatment effects from these 100 MMRM analyses were then combined using Rubin's Method (100) via the SAS PROC MIANALYZE procedure. The difference in the least squares means between treatment groups and corresponding two-sided 95% CI was provided for hypothesis testing.

B.2.4.6 Statistical analysis of secondary endpoints

The secondary efficacy endpoints were not to be tested if either or both co-primary efficacy endpoints' null hypotheses failed to be rejected.

The key secondary endpoints of the studies were:

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

The Hochberg procedure (101) was applied to control the family-wise type I error rate at a two-sided significance level of alpha=0.05 for the key secondary endpoints.

Missing values were imputed using the control-based PMM (Section B.2.4.4.1) on LDL-C, PCSK9, total cholesterol, Apo-B, and non-HDL-C; absolute change or percentage change from baseline was calculated based on imputed data before any analysis was performed.

The absolute change in LDL-C from 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 covariates. Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540 was analysed similarly to that of time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540.

MMRM without multiple imputation was used as sensitivity analyses for the key secondary endpoints.

Other secondary endpoints were analysed as follows:

- The two-sided 95% CI for LSM was provided for continuous variables at a single point using an analysis of covariance model or using MMRM methods for variables measured over time.
- The odds ratio (OR) and 95% CI for the OR was provided for binary variables using logistic regression models. Nominal p-values were provided when applicable.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Appendix D contains the quality assessment of each of the trials identified in the SLR.

B.2.6 Clinical effectiveness results of the relevant trials

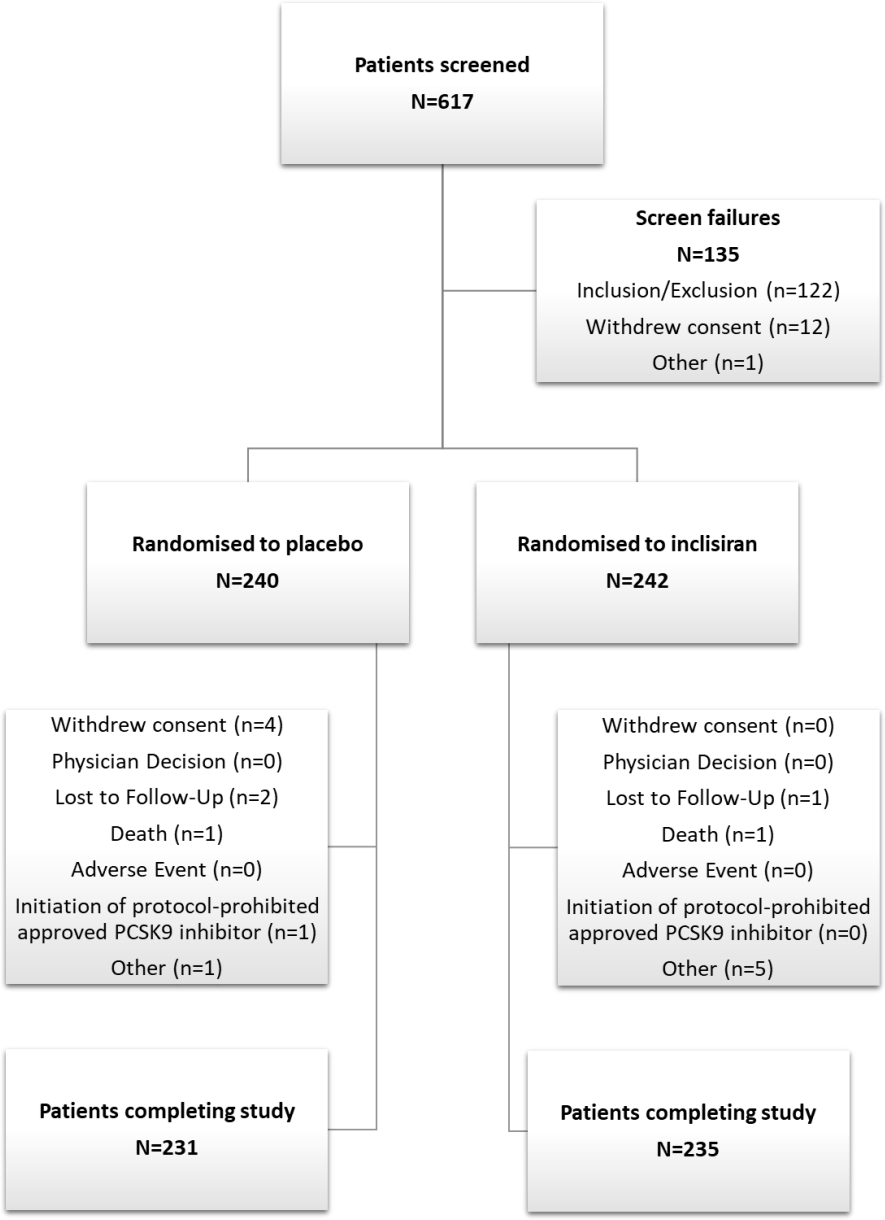
All ORION phase III clinical trials met their co-primary endpoints, demonstrating that after two starter doses, twice-yearly subcutaneous dosing with inclisiran resulted in sustained and effective LDL-C reductions vs placebo. Results for each trial are presented separately in Sections B.2.6.1–B.2.6.3.

B.2.6.1 ORION-9

B.2.6.1.1 *Patient disposition*

The flow of patients in ORION-9 is presented in Figure 6, and a summary of analysis populations (defined in Section B.2.4.3) is provided in Table 13.

Figure 6: Flow of patients (ORION-9)



Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 13: Analysis populations (ORION-9)

Analysis population	Placebo (N=240)	Inclisiran (N=242)	Total (N=482)
Randomised	240	242	482
ITT	240	242	482
FAS	239	241	480
mITT	229	231	460
Safety	240	241	481

Abbreviations: FAS, full analysis set; ITT, intention-to-treat; mITT, modified intention-to-treat.

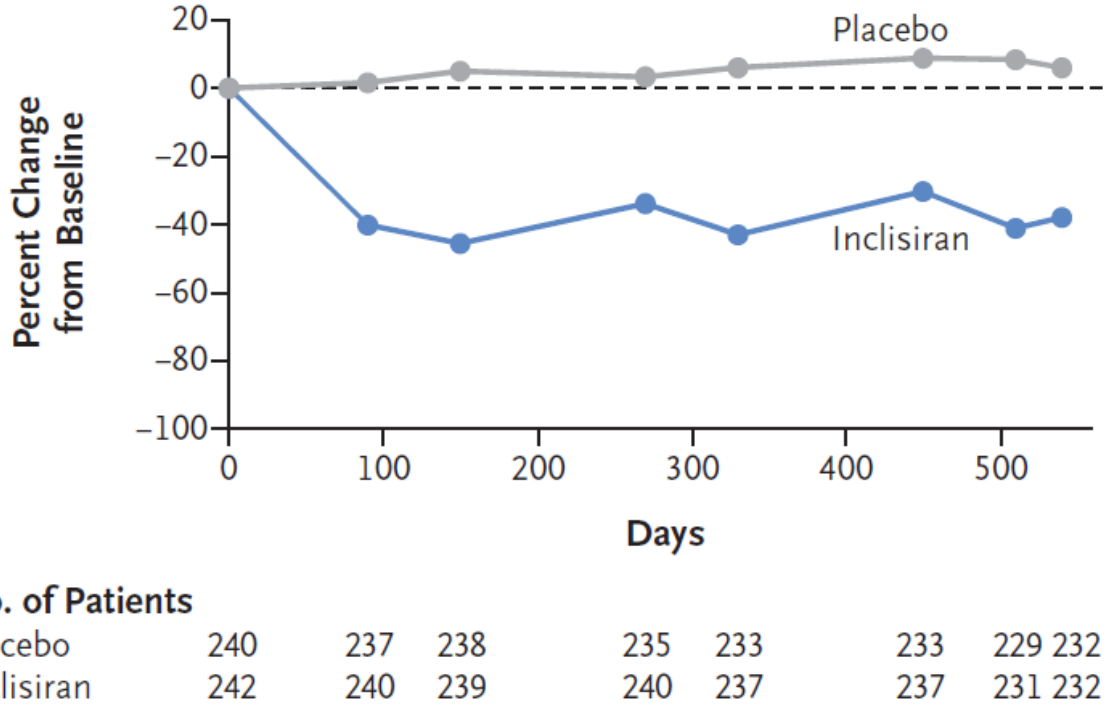
B.2.6.1.2 *Co-primary endpoints*

B.2.6.1.2.1 Percentage change in LDL-C from baseline to Day 510

The percentage change in the LDL-C level from baseline to Day 510 using a multiple imputation washout model was a decrease of 39.7% (95% CI −43.7 to −35.7) in the inclisiran group and an increase of 8.2% (95% CI 4.3 to 12.2) in the placebo group, for a between-group difference of −47.9% (95% CI −53.5 to −42.3; p<0.001).

The mean percentage change in LDL-C using LSM is presented in Figure 7.

Figure 7: Observed mean percentage change from baseline LDL-C by visit (ITT population; ORION-9)



Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.1.2.2 Time-adjusted percentage change from baseline after Day 90 and up to Day 540

The time-adjusted percentage change in the LDL-C level between Day 90 and Day 540 using a control-based PMM was a decrease of 38.1% (95% CI −41.1 to −35.1) in the inclisiran group and an increase of 6.2% (95% CI 3.3 to 9.2) in the placebo group, for a between-group difference of −44.3% (95% CI −48.5 to −40.1; p<0.001).

B.2.6.1.2.3 Analysis populations

Analysis of the co-primary endpoints using the FAS and mITT populations (Section B.2.4.3) produced similar statistically significant placebo-adjusted differences (p<0.0001).

B.2.6.1.2.4 Sensitivity analyses

Three additional, pre-specified sensitivity analyses (PMM, MMRM, ANCOVA with country as a covariate) for handling missing values were performed. Similar and statistically significant (p<0.0001) placebo-adjusted differences were observed for both co-primary endpoints, regardless of sensitivity analysis used to handle missing values (Table 14 and Table 15).

Table 14: Sensitivity analyses of percentage change in LDL-C from baseline to Day 510 (ITT population; ORION-9)

	Placebo (N=240)	Inclisiran (N=242)	p-value
Control-based PMM†			
LSM (95% CI)	8.27 (4.32, 12.23)	–39.71 (–43.69, –35.73)	
LSM difference (95% CI) from placebo		–47.98 (–53.59, –42.38)	<0.0001
MMRM‡			
LSM (95% CI)	8.06 (4.16, 11.96)	–40.76 (–44.63, –36.88)	
LSM difference (95% CI) from placebo		–48.82 (–54.32, –43.32)	<0.0001
ANCOVA from multiple imputation washout model including country¶			
LSM (95% CI)	8.44 (2.99, 13.88)	–39.46 (–44.74, –34.19)	
LSM difference (95% CI) from placebo		–47.90 (–55.47, –40.33)	<0.0001

†A control-based PMM was used for missing data imputation with 100 total imputed datasets. An MMRM on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, current use of statins or other lipid lowering therapies (yes/no), and baseline LDL-C as a covariate

‡An MMRM analysis that assumes missing data are MAR was performed.

¶A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. ANCOVA on each of the 100 datasets was performed by including fixed effects for treatment, current use of statins or other lipid lowering therapies (yes/no), country, interaction between treatment and country, and baseline LDL-C as a covariate. Treatment effects from the 100 analyses were combined using Rubin's method.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LSM, least squares mean; MAR, missing at random; MMRM, mixed-effects model for repeated measures; PMM, pattern-mixture model.

Table 15: Sensitivity analyses of time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 (ITT population; ORION-9)

	Placebo (N=240)	Inclisiran (N=242)	p-value
MMRM[†]			
LSM (95% CI)	6.27 (3.34, 9.20)	–38.49 (–41.40, –35.59)	
LSM difference (95% CI) from placebo		–44.76 (–48.89, –40.64)	<0.0001
Control-based PMM including country[‡]			
LSM (95% CI)	5.06 (1.09, 9.02)	–36.80 (–40.54, –33.06)	
LSM difference (95% CI) from placebo		–41.86 (–47.31, –36.41)	<0.0001
Two sample t-test[¶]			
LSM (95% CI)	6.14 (2.86, 9.43)	–38.01 (–40.61, –35.41)	
LSM difference (95% CI) from placebo		–44.15 (–48.34, –39.96)	<0.0001

[†]An MMRM analysis that assumes missing data are MAR was performed. The model included fixed effects for treatment, visit, interaction between treatment and visit, current use of statins or other lipid lowering therapies (yes/no), and baseline LDL-C as a covariate.
[‡]A control-based PMM was used for missing data imputation with 100 total imputed datasets.
[¶]The time-adjusted percentage change was calculated by taking the arithmetic mean of calculated percentage change in LDL-C from baseline at each visit after Day 90 through Day 540.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LSM, least squares mean; MAR, missing at random; MMRM, mixed-effects model for repeated measures; PMM, pattern-mixture model.

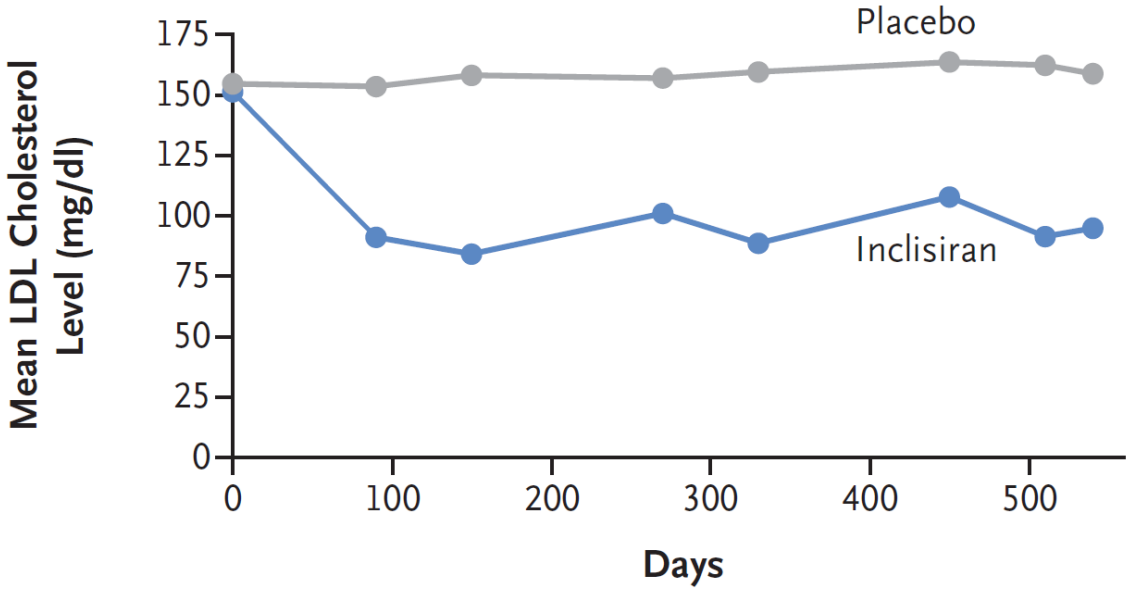
B.2.6.1.3 *Key secondary endpoints*

B.2.6.1.3.1 Absolute change in LDL-C from baseline to Day 510

The absolute change in LDL-C level at Day 510 using a control-based PMM was an increase of 0.3 mmol/l in the placebo group and a decrease of 1.5 mmol/l in the inclisiran group, for a between-group difference of −1.8 mmol/l (95% CI −2.0 to −1.6 mmol/l; p<0.001).

The absolute change in LDL-C using least squares means is presented in Figure 8.

Figure 8: Observed absolute change in LDL-C by visit (ITT population; ORION-9)



No. of Patients								
Placebo	240	237	238	235	233	233	229	232
Inclisiran	242	240	239	240	237	237	231	232

Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.1.3.2 Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540

The time-adjusted absolute change in LDL-C level from Day 90 to Day 540 using a control-based PMM was an increase of 0.1 mmol/l in the placebo group and a decrease of 1.5 mmol/l in the inclisiran group, for a between-group difference of −1.6 mmol/l (95% CI, −1.44 to −1.31 mmol/l; p<0.001).

B.2.6.1.3.3 Percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B, and non-HDL-C

Significant reductions were observed in PCSK9, total cholesterol, Apo-B and non-HDL-C (p<0.0001 for all comparisons). Percentage changes calculated using a control-based PMM are shown in Table 16.

Table 16: Percentage change in PCSK9, total cholesterol, Apo-B and non-HDL-C from baseline to Day 510 (ITT population; ORION-9)

	Placebo (N=240)	Inclisiran (N=242)	p-value
PCSK9			
LSM (95% CI)	17.66 (13.91, 21.42)	–60.68 (–64.40, –56.96)	
LSM difference (95% CI) from placebo		–78.34 (–83.65, –73.04)	<0.0001
Total cholesterol			
LSM (95% CI)	6.66 (3.96, 9.36)	–25.11 (–27.83, –22.39)	
LSM difference (95% CI) from placebo		–31.77 (–35.59, –27.94)	<0.0001
Apo-B			
LSM (95% CI)	2.93 (0.14, 5.71)	–33.14 (–35.91, –30.36)	
LSM difference (95% CI) from placebo		–36.06 (–39.99, –32.14)	<0.0001
Non-HDL-C			
LSM (95% CI)	7.43 (3.93, 10.92)	–34.93 (–38.46, –31.40)	
LSM difference (95% CI) from placebo		–42.36 (–47.32, –37.40)	<0.0001

Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LSM, least squares mean; PCSK9, proprotein convertase subtilisin/kexin type 9

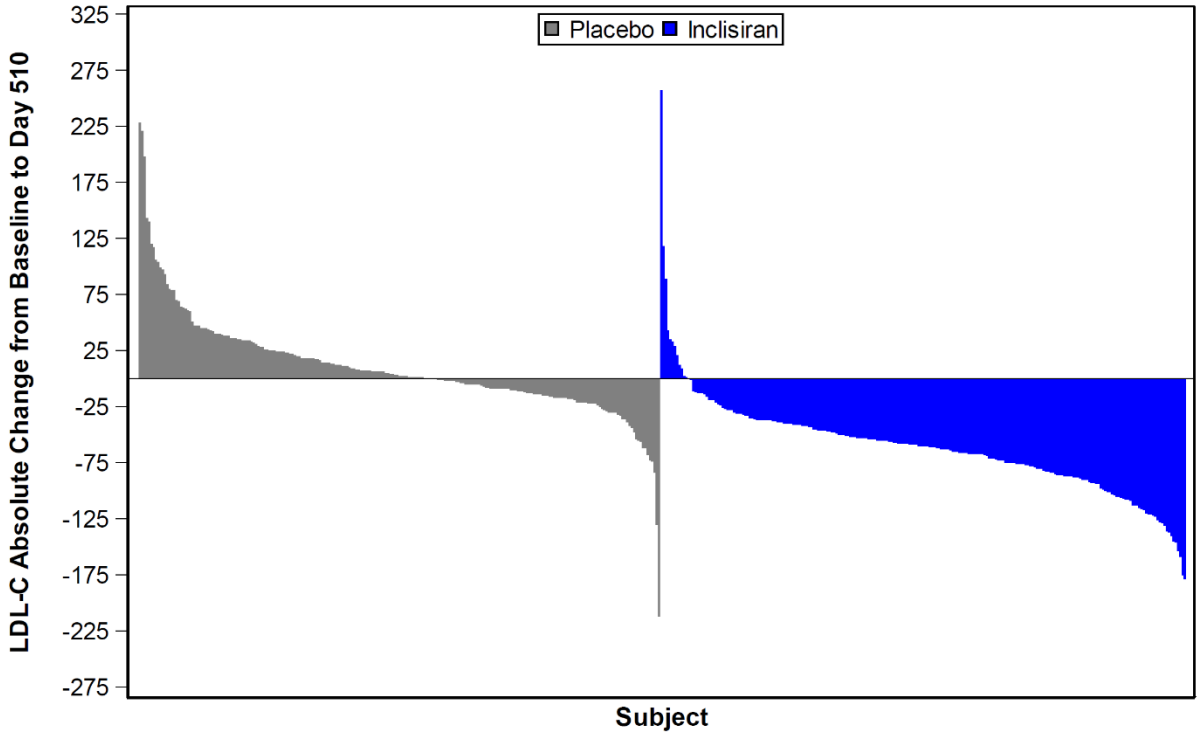
B.2.6.1.4 *Other secondary endpoints*

B.2.6.1.4.1 Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540

The placebo-adjusted percentage reduction in LDL-C from baseline ranged between 37.2% to 50.5% at all time points up to Day 540 (observed values, p<0.0001 for all time points). The results were similar regardless of analysis population (ITT, FAS, mITT).

A waterfall plot of absolute change in LDL-C from baseline to Day 510 is provided in Figure 9.

Figure 9: Waterfall plot of absolute change in LDL-C from baseline to day 510 (ITT population; ORION-9)



Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.1.4.2 Absolute change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B and non-HDL-C

The placebo-adjusted change in PCSK9, total cholesterol, Apo-B and non-HDL-C from baseline to Day 510 were all statistically significant (p<0.0001) (Table 17). The results were similar regardless of analysis population used (ITT, FAS, mITT).

Table 17: Absolute change from baseline to day 510 in PCSK9, total cholesterol, apo-b and non-HDL-C using ANCOVA† (ITT population; ORION-9)

	Placebo (N=240)	Inclisiran (N=242)	p-value
PCSK9 (ug/L)			
LSM (95% CI)	54.54 (39.11,69.97)	-282.6 (-297.9, -267.2)	
LSM difference (95% CI) from placebo		-337.1 (-358.9, 315.3)	<0.0001
Total cholesterol (mg/dl)			
LSM (95% CI)	12.63 (6.44,18.81)	-60.84 (-66.99, -54.68)	
LSM difference (95% CI) from placebo		-73.46 (-82.18, -64.74)	<.0001

	Placebo (N=240)	Inclisiran (N=242)	p-value
Apolipoprotein B (mg/dl)			
LSM (95% CI)	1.86 (-1.64,5.35)	-42.48 (-45.96, -38.99)	
LSM difference (95% CI) from placebo		-44.33 (-49.27, -39.40)	<.0001
Non-HDL Cholesterol calculated (mg/dl)			
LSM (95% CI)	10.30 (4.14,16.47)	-64.31 (-70.45, -58.17)	
LSM difference (95% CI) from placebo		-74.61 (-83.31, -65.91)	<.0001

†ANCOVA including fixed effects for treatment and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HDL, high density lipoprotein; ITT, intention-to-treat; LSM, least squares mean; PCSK9; proprotein convertase subtilisin/kexin type 9.

B.2.6.1.4.3 Individual responsiveness defined as the number of patients reaching on-treatment LDL-C levels of <25 mg/dl, <50 mg/dl, <70 mg/dl, and <100 mg/dl at Day 510

At Day 510, 65.3% (158/242) of inclisiran-treated patients reached an LDL-C level of <100 mg/dl compared with 8.8% (21/240) of placebo-treated patients. The number of patients achieving defined threshold levels is presented in Table 18.

Table 18: Individual responsiveness as measured by LDL-C levels at day 510† (ITT population; ORION-9)

LDL-C (mg/dl) levels	Placebo (N=240) n (%)	Inclisiran (N=242) n (%)
<25 mg/dl	0 (0.0)	2 (0.8)
<50 mg/dl	2 (0.8)	46 (19.0)
<70 mg/dl	3 (1.3)	99 (40.9)
<100 mg/dl	21 (8.8)	158 (65.3)
≥100 mg/dl	208 (86.7)	73 (30.2)
Missing	11 (4.6)	11 (4.5)

†Patients can be counted in multiple categories.
Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.1.4.4 Proportion of patients in each group with greater or equal to 50% LDL-C reduction from baseline

At any time during the study, 66.0% (159/241) of inclisiran-treated patients had ≥50% LDL-C reduction from baseline compared with 3.8% (9/239) of placebo-treated patients (Table 19).

Table 19: Proportion of patients in each group with greater or equal to 50% LDL-C reduction from baseline (ITT Population; ORION-9)

LDL-C (mg/dl) levels	Placebo (N=240) n/N (%)	Inclisiran (N=242) n/N (%)
Number of patients reaching LDL-C level ≥50%		
Reduction from baseline at any visit	9/239 (3.8)	159/241 (66.0)
Number of patients reaching LDL-C level ≥50%		
Reduction from baseline at†:		
Visit 3 Day 90	6/237 (2.5)	81/240 (33.8)
Visit 4 Day 150	4/238 (1.7)	116/239 (48.5)
Visit 5 Day 270	5/235 (2.1)	50/240 (20.8)
Visit 6 Day 330	4/233 (1.7)	101/237 (42.6)
Visit 7 Day 450	1/233 (0.4)	48/237 (20.3)
Visit 8 Day 510	2/229 (0.9)	92/231 (39.8)
Visit 9 Day 540	4/232 (1.7)	85/232 (36.6)

†Only patients with LDL-C values at a given visit are included in that visit.
Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.1.4.5 Proportion of patients in each group who attain global lipid targets for their level of ASCVD risk

At any visit, 77.2% (186/241) of inclisiran-treated patients achieved their corresponding LDL-C targets compared with 18.4% (44/239) of placebo-treated patients. At Day 510, 52.5% (31/59) of inclisiran-treated patients with ASCVD achieved their LDL-C target of <70 mg/dl compared with 1.4% (1/71) of placebo-treated patients with ASCVD. At Day 510, 66.9% (115/172) of inclisiran-treated patients with ASCVD risk-equivalent achieved their LDL-C target of <100 mg/dl compared with 8.9% (14/158) of placebo-treated ASCVD risk-equivalent patients. Similar results were observed at all other time points.

B.2.6.1.4.6 Absolute change and percentage change in lipoprotein-a from baseline to Day 540

Inclisiran lowered lipoprotein-a levels from baseline through Day 540 (Table 20).

Table 20: Absolute and percentage change from baseline to Day 540 in lipoprotein-a using MMRM† (ITT population; ORION-9)

	Placebo (N=240)	Inclisiran (N=242)	p-value
Absolute change (nmol/L)			
LSM (95% CI)	-0.1 (-4.1, 3.9)	-16.0 (-20.0, -12.0)	
LSM difference (95% CI) from placebo		-15.9 (-21.5, -10.3)	<.0001
Percentage change (%)			
LSM (95% CI)	7.6 (3.8, 11.4)	-11.9 (-15.7, -8.1)	
LSM difference (95% CI) from placebo		-19.5 (-24.9, -14.1)	<.0001

†MMRM including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LSM, least squares mean; MMRM, mixed-effect models for repeated measures.

B.2.6.1.4.7 Absolute change and percentage change in other lipids, lipoproteins, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540

Inclisiran lowered PCSK9 levels from baseline through Day 540. In addition, changes in apolipoprotein A1, Apo B, TC, C-reactive protein, HDL-C, non-HDL-C, triglycerides, and VLDL-C, were consistent with the changes observed in LDL-C and PCSK9. These observations were similar regardless of analysis population used (ITT, FAS, mITT).

B.2.6.1.4.8 Maximum percentage change in LDL-C

The placebo-adjusted mean maximum (based on individual patient's maximum reduction) percent change in LDL-C from baseline was 66.9% (p<0.0001). The results were statistically significant (p<0.0001) and similar regardless of analysis population used (ITT, FAS, mITT).

B.2.6.1.5 *Exploratory endpoints*

B.2.6.1.5.1 MACE defined as the composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic or haemorrhagic) using a broad basket MedDRA terms to identify events.

The proportion of patients with a MACE event was the same for inclisiran-treated patients (4.1%; 10/241) and placebo-treated patients (4.2%; 10/240) during the course of the study.

B.2.6.1.5.2 Proportion of patients in each group with any LDL-C reduction from baseline at any visit (responders).

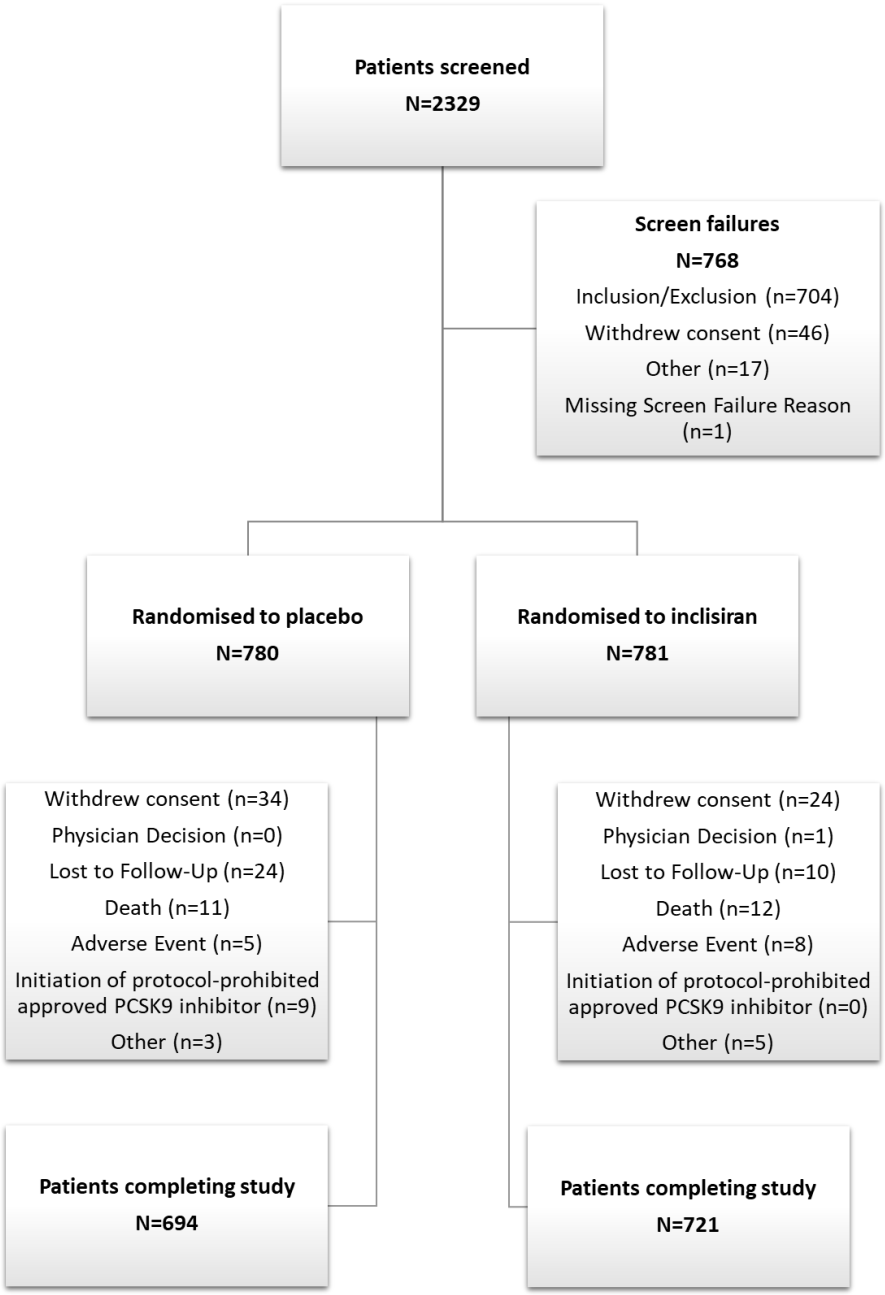
All but two patients (99.2%; 239/241) responded to inclisiran by having a reduction in LDL-C at any time during study. These two non-responders both had post-baseline reductions in PCSK9.

B.2.6.2 ORION-10

B.2.6.2.1 *Patient disposition*

The flow of patients in ORION-10 is presented in Figure 10, and a summary of analysis populations (defined in Section B.2.4.3) is provided in Table 21.

Figure 10: Flow of patients (ORION-10)



Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 21: Analysis populations (ORION-10)

Analysis population	Placebo (N=780)	Inclisiran (N=781)	Total (N=1,561)
Randomised	780	781	1,561
ITT	780	781	1,561
FAS	768	767	1,535
mITT	666	691	1,357
Safety	778	781	1,559

Abbreviations: FAS, full analysis set; ITT, intention-to-treat; mITT, modified intention-to-treat.

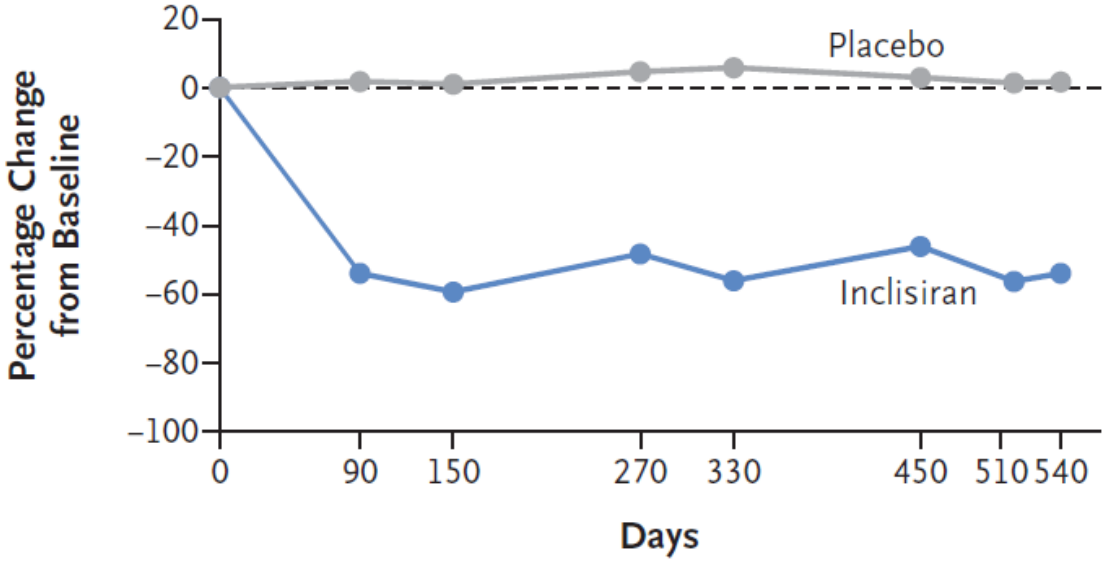
B.2.6.2.2 *Co-primary endpoints*

B.2.6.2.2.1 Percentage change in LDL-C from baseline to Day 510

The percentage change in the LDL-C level at Day 510 using a multiple imputation washout model was a decrease of 51.3% (95% CI –53.8 to –48.8) in the inclisiran group and an increase of 1.0% (95% CI –1.5 to 3.4) in the placebo group, for a between-group difference of −52.3% (95% CI −55.7 to −48.8; p<0.001).

The mean percentage change in LDL-C using least squares means is presented in Figure 11.

Figure 11: Observed mean percentage change from baseline LDL-C by visit (ITT population; ORION-10)



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

Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.2.2.2 Time-adjusted percentage change from baseline after Day 90 and up to Day 540

The time-adjusted percentage change in the LDL-C level between Day 90 and Day 540 using a control-based PMM was a decrease of 51.3% (95% CI −53.0 to −49.5) in the inclisiran group and an increase of 2.5% (95% CI 0.8 to 4.3) in the placebo group, for a between-group difference of −53.8% (95% CI −56.2 to −51.3; p<0.001).

B.2.6.2.2.3 Analysis populations

Analysis of the co-primary endpoints using the FAS and mITT populations (Section B.2.4.3) produced similar statistically significant placebo-adjusted differences (p<0.0001).

B.2.6.2.2.4 Sensitivity analyses

Three additional, pre-specified sensitivity analyses (PMM, MMRM, ANCOVA with current use of statins or other LLTs as fixed effects) for handling missing values were performed. Similar and statistically significant (p<0.0001), placebo-adjusted differences were observed for both co-primary endpoints, regardless of sensitivity analysis used to handle missing values (Table 22 and Table 23).

Table 22: Sensitivity analyses of percentage change in LDL-C from baseline to Day 510 (ITT population; ORION-10)

	Placebo (N=780)	Inclisiran (N=781)	p-value
Control-based PMM†			
LSM (95% CI)	1.01 (–1.32,3.35)	–53.45 (–55.77, –51.12)	
LSM difference (95% CI) from placebo		–54.46 (–57.77, –51.15)	<0.0001
MMRM‡			
LSM (95% CI)	1.07 (–1.15,3.29)	–56.17 (–58.36, –53.98)	
LSM difference (95% CI) from placebo		–57.24 (–60.36, –54.13)	<0.0001
ANCOVA from multiple imputation washout model including current use of statin/LLT¶			
LSM (95% CI)	6.78 (2.99,10.56)	–45.49 (–49.31, –41.67)	
LSM difference (95% CI) from placebo		–52.27 (–55.66, –48.87)	<0.0001

†A control-based PMM was used for missing data imputation with 100 total imputed datasets. An MMRM on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate
‡An MMRM analysis that assumes missing data are MAR was performed.
¶A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. ANCOVA on each of the 100 datasets was performed by including fixed effects for treatment, current use of statins or other lipid lowering therapies(y/n), and baseline LDL-C as a covariate. Treatment effects from the 100 analyses were combined using Rubin's method.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; LSM, least squares mean; MMRM, mixed-effects model for repeated measures; PMM, pattern-mixture model

Table 23: Sensitivity analyses of time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 (ITT population; ORION-10)

	Placebo (N=780)	Inclisiran (N=781)	p-value
MMRM†			
LSM (95% CI)	2.72 (1.06,4.39)	–53.15 (–54.79, –51.50)	
LSM difference (95% CI) from placebo		–55.87 (–58.21, –53.53)	<0.0001
Control-based PMM including current use of statin/LLT‡			
LSM (95% CI)	7.47 (4.89,10.05)	–46.33 (–48.91, –43.76)	
LSM difference (95% CI) from placebo		–53.80 (–56.23, –51.37)	<0.0001
Two sample t-test¶			
LSM (95% CI)	2.50 (0.63,4.37)	–51.25 (–52.89, –49.62)	
LSM difference (95% CI) from placebo		–53.75 (–56.24, –51.27)	<0.0001

†An MMRM analysis that assumes missing data are MAR was performed. The model included fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate.
‡A control-based PMM was used for missing data imputation with 100 total imputed datasets. An MMRM on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, current use of statins or other lipid lowering therapies (y/n), and baseline LDL-C as a covariate
¶The time-adjusted percentage change was calculated by taking the arithmetic mean of calculated percentage change in LDL-C from baseline at each visit after Day 90 through Day 540.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; LSM, least squares mean; MMRM, mixed-effects model for repeated measurements; PMM, pattern-mixture model

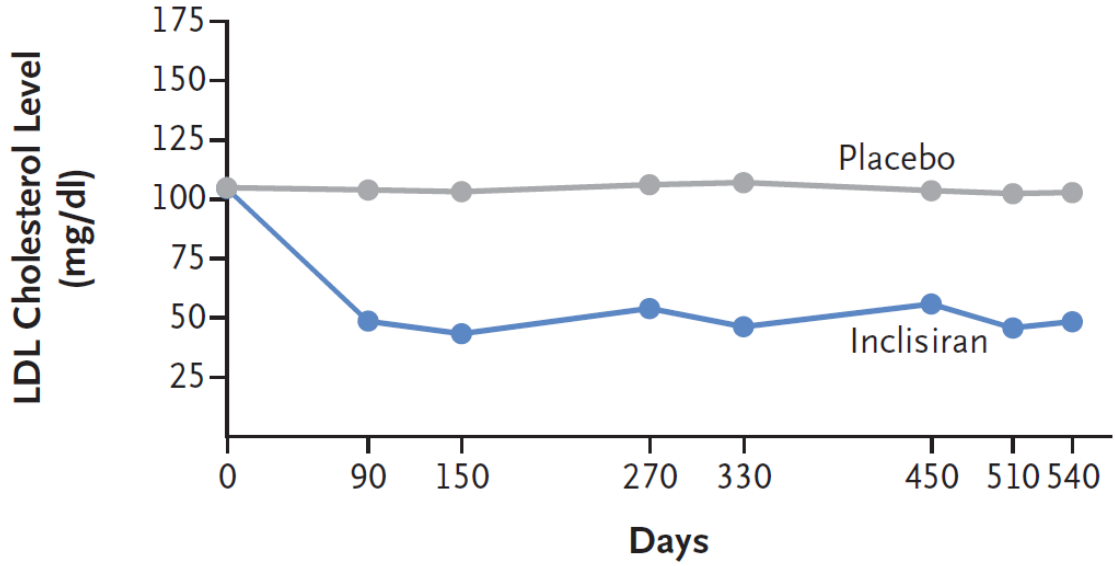
B.2.6.2.3 *Key secondary endpoints*

B.2.6.2.3.1 Absolute change in LDL-C from baseline to Day 510

The absolute change in LDL-C level at Day 510 using a control-based PMM was a decrease of 0.05 mmol/l in the placebo group and a decrease of 1.45 mmol/l in the inclisiran group, for a between-group difference of −1.40 mmol/l (95% CI −1.48 to −1.32 mmol/l; p<0.001).

The absolute change in LDL-C using least squares means is presented in Figure 12.

Figure 12: Observed absolute change in LDL-C by visit (ITT population; ORION-10)



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

Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.2.3.2 Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540

The time-adjusted absolute change in LDL-C level from Day 90 to Day 540 using a control-based PMM was a decrease of 0.01 mmol/l in the placebo group and a decrease of 1.39 mmol/l in the inclisiran group, for a between-group difference of −1.38 mmol/l (95% CI, −1.44 to −1.31 mmol/l; p<0.001).

B.2.6.2.3.3 Percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B, and non-HDL-C

Significant reductions were observed in PCSK9, total cholesterol, Apo-B and non-HDL-C (p<0.0001 for all comparisons). Percentage changes calculated using a control-based PMM are shown in Table 24.

Table 24: Percentage change in PCSK9, total cholesterol, Apo-B and non-HDL-C from baseline to Day 510 (ITT population; ORION-10)

	Placebo (N=780)	Inclisiran (N=781)	p-value
PCSK9			
LSM (95% CI)	13.52 (9.28,17.77)	–69.78 (–73.88, –65.67)	
LSM difference (95% CI) from placebo		–83.30 (–89.25, –77.34)	<0.0001
Total cholesterol			
LSM (95% CI)	–0.42 (–1.95,1.11)	–33.56 (–35.09, –32.03)	
LSM difference (95% CI) from placebo		–33.13 (–35.30, –30.97)	<0.0001
Apo-B			
LSM (95% CI)	–1.72 (–3.46,0.02)	–44.81 (–46.52, –43.10)	
LSM difference (95% CI) from placebo		–43.09 (–45.50, –40.67)	<0.0001
Non-HDL-C			
LSM (95% CI)	–0.05 (–2.08,1.99)	–47.41 (–49.44, –45.38)	
LSM difference (95% CI) from placebo		–47.36 (–50.25, –44.47)	<0.0001

Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LSM, least squares mean; PCSK9, proprotein convertase subtilisin/kexin type 9

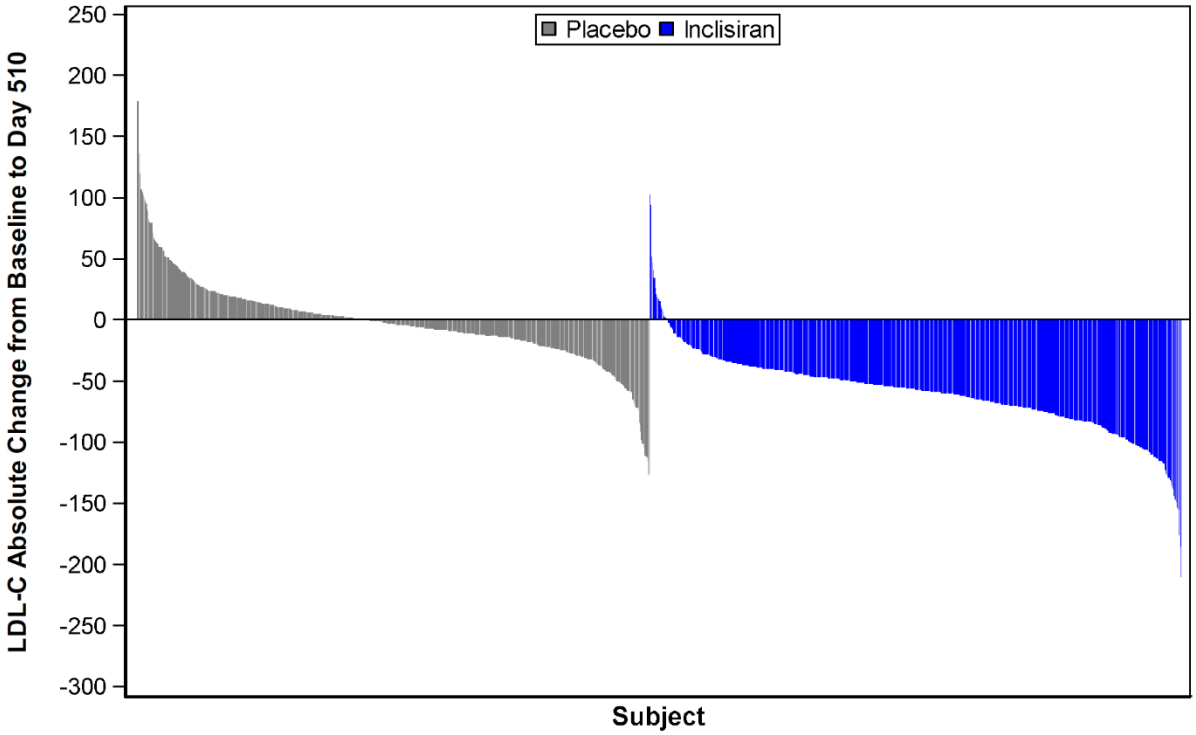
B.2.6.2.4 *Other secondary endpoints*

B.2.6.2.4.1 Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540

The placebo-adjusted percentage reduction in LDL-C from baseline ranged between 48.5% to 61.4% at all time points up to Day 540 (observed values, p<0.0001 for all time points). The results were similar regardless of analysis population (ITT, FAS, mITT).

A waterfall plot of absolute change in LDL-C from baseline to Day 510 is provided in Figure 13. All but three patients (99.6%; 762/765) responded to inclisiran by having a reduction in LDL-C at any time during study. All three patients had significant responses in PCSK9 levels.

Figure 13: Waterfall plot of absolute change in LDL-C from baseline to day 510 (ITT population; ORION-10)



Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.2.4.2 Absolute change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B and non-HDL-C

The placebo-adjusted change in PCSK9, total cholesterol, Apo-B and non-HDL-C from baseline to Day 510 were all statistically significant (p<0.0001) (Table 25) The results were similar regardless of analysis population used (ITT, FAS, mITT).

Table 25: Absolute change from baseline to day 510 in PCSK9, total cholesterol, Apo-b and non-HDL-C using ANCOVA† (ITT population; ORION-10)

	Placebo (N=780)	Inclisiran (N=781)	p-value
PCSK9 (ug/L)			
LSM (95% CI)	17.87 (5.59, 30.15)	–316.1 (–328.1, –304.0)	
LSM difference (95% CI) from placebo		–333.9 (–351.1, –316.7)	<0.0001
Total Cholesterol (mg/dl)			
LSM (95% CI)	–3.20 (–5.91, –0.49)	–64.76 (–67.42, –62.10)	
LSM difference (95% CI) from placebo		–61.55 (–65.35, –57.76)	<0.0001

	Placebo (N=780)	Inclisiran (N=781)	p-value
Apolipoprotein B (mg/dl)			
LSM (95% CI)	–3.08 (–4.66, –1.49)	–44.74 (–46.30, –43.18)	
LSM difference (95% CI) from placebo		–41.66 (–43.89, –39.44)	<0.0001
Non-HDL Cholesterol calculated (mg/dl)			
LSM (95% CI)	–3.11 (–5.75, –0.47)	–67.31 (–69.90, –64.72)	
LSM difference (95% CI) from placebo		–64.20 (–67.89, –60.50)	<0.0001

†ANCOVA including fixed effects for treatment and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HDL, high density lipoprotein; ITT, intention-to-treat; LSM, least squares mean; PCSK9; proprotein convertase subtilisin/kexin type 9.

B.2.6.2.4.3 Individual responsiveness defined as the number of patients reaching on-treatment LDL-C levels of <25 mg/dl, <50 mg/dl, <70 mg/dl, and <100 mg/dl at Day 510

At Day 510, 83.4% (651/781) of inclisiran-treated patients reached an LDL-C level of <100 mg/dl compared with 49.6% (387/780) of placebo-treated patients. The number of patients achieving defined threshold levels is presented in Table 26.

Table 26: Individual responsiveness as measured by LDL-C levels at Day 510† (ITT population; ORION-10)

LDL-C (mg/dl) levels	Placebo (N=780) (%)	Inclisiran (N=781) (%)
<25 mg/dl	4 (0.5)	160 (20.5)
<50 mg/dl	19 (2.4)	483 (61.8)
<70 mg/dl	119 (15.3)	581 (74.4)
<100 mg/dl	387 (49.6)	651 (83.4)
≥100 mg/dl	279 (35.8)	40 (5.1)
Missing	114 (14.6)	90 (11.5)

†Patients can be counted in multiple categories.
Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.2.4.4 Proportion of patients in each group with greater or equal to 50% LDL-C reduction from baseline

At any time during the study, 91.4% (701/767) of inclisiran-treated patients had ≥50% LDL-C reduction from baseline compared with 6.5% (50/767) of placebo-treated patients (Table 27).

Table 27: Proportion of patients in each group with greater or equal to 50% LDL-C reduction from baseline (ITT Population; ORION-10)

LDL-C (mg/dl) levels	Placebo (N=780) n/N (%)	Inclisiran (N=781) n/N (%)
Number of patients reaching LDL-C level ≥50%		
Reduction from baseline at any visit	50/767 (6.5)	701/767 (91.4)
Number of patients reaching LDL-C level ≥50%		
Reduction from baseline at†:		
Visit 3 Day 90	13/762 (1.7)	503/758 (66.4)
Visit 4 Day 150	17/745 (2.3)	584/757 (77.1)
Visit 5 Day 270	17/724 (2.3)	391/737 (53.1)
Visit 6 Day 330	14/715 (2.0)	513/731 (70.2)
Visit 7 Day 450	18/698 (2.6)	382/721 (53.0)
Visit 8 Day 510	17/666 (2.6)	503/691 (72.8)
Visit 9 Day 540	18/670 (2.7)	482/705 (68.4)

†Only patients with LDL-C values at a given visit are included in that visit.
Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.2.4.5 Proportion of patients in each group who attain global lipid targets for their level of ASCVD risk

At any visit, 94.1% (722/767) of inclisiran-treated patients achieved their corresponding LDL-C targets compared with 36.1% (277/767) of placebo-treated patients. At Day 510, 84.1% (581/691) of inclisiran-treated patients with ASCVD achieved their LDL-C target of <70 mg/dl compared with 17.9% (119/666) of placebo-treated patients with ASCVD.

B.2.6.2.4.6 Absolute change and percentage change in lipoprotein-a from baseline to Day 540

Inclisiran lowered lipoprotein-a levels from baseline through Day 540 (Table 28).

Table 28: Absolute and percentage change from baseline to Day 540 in lipoprotein-a using MMRM† (ITT population; ORION-10)

	Placebo (N=780)	Inclisiran (N=781)	p-value
Absolute change (nmol/L)			
LSM (95% CI)	0.5 (-2.3, 3.3)	-25.9 (-28.7, -23.2)	
LSM difference (95% CI) from placebo		-26.4 (-30.3, -22.5)	<.0001

	Placebo (N=780)	Inclisiran (N=781)	p-value
Percentage change (%)			
LSM (95% CI)	16.4 (12.6, 20.2)	-15.5 (-19.2, -11.8)	
LSM difference (95% CI) from placebo		-31.9 (-37.2, -26.5)	<.0001

†MMRM including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LSM, least squares mean; MMRM, mixed-effect models for repeated measures.

B.2.6.2.4.7 Absolute change and percentage change in other lipids, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540

Inclisiran lowered PCSK9 levels from baseline through Day 540. In addition, changes in apolipoprotein A1, apolipoprotein B, total cholesterol, C-reactive protein, HDL cholesterol, non-HDL cholesterol, triglycerides, VLDL cholesterol, and VLDL cholesterol were consistent with the changes observed in LDL-C and PCSK9. These observations were similar regardless of analysis population used (ITT, FAS, mITT).

B.2.6.2.4.8 Maximum percentage change in LDL-C

The placebo-adjusted mean maximum (based on individual patient's maximum reduction) percent change in LDL-C from baseline was 77.2% (p<0.0001). The results were statistically significant (p<0.0001) and similar regardless of analysis population used (ITT, FAS, mITT).

B.2.6.2.5 *Exploratory endpoints*

B.2.6.2.5.1 MACE defined as the composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic or haemorrhagic) using a pre-defined MedDRA search to identify events.

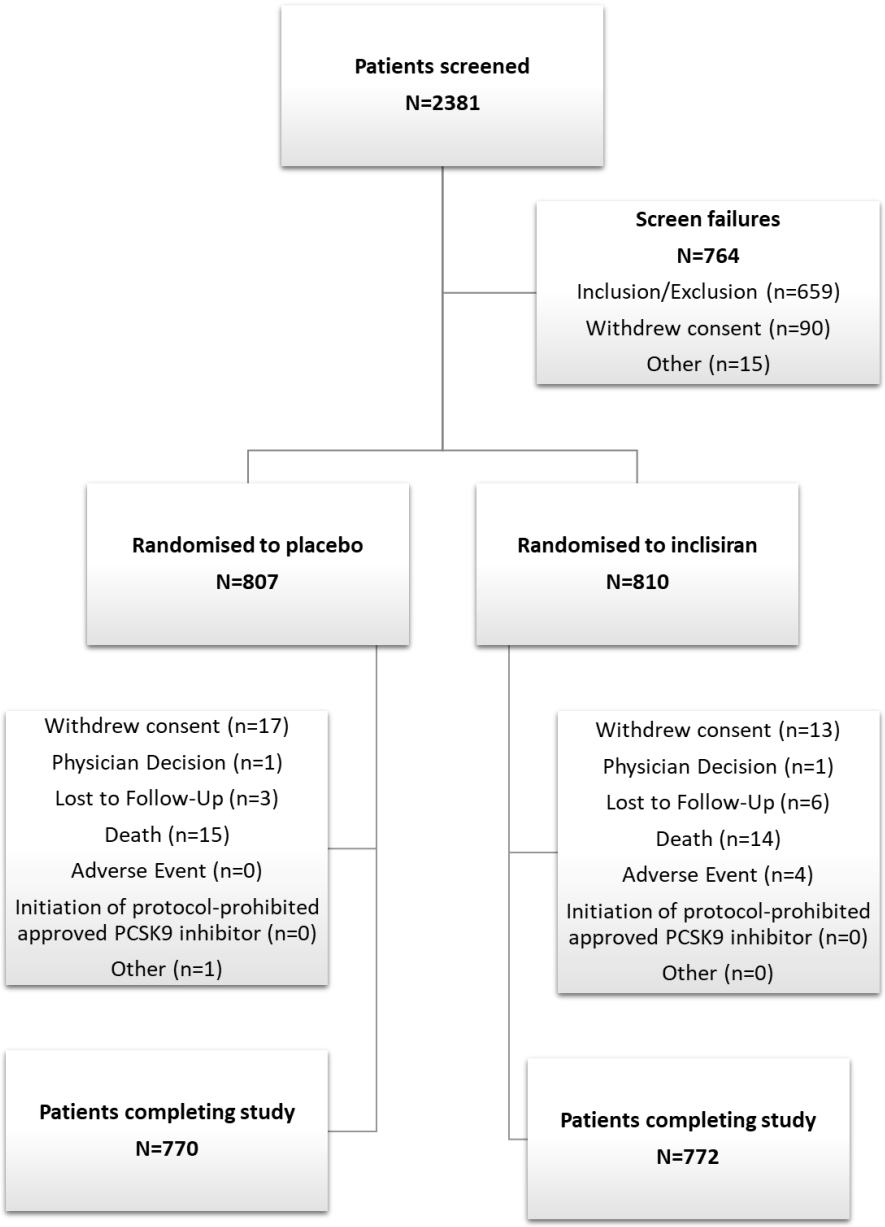
The proportion of patients with a MACE event was 10.2% (79/778) in placebo-treated patients compared with 7.4% (58/781) in inclisiran-treated patients.

B.2.6.3 ORION-11

B.2.6.3.1 *Patient disposition*

The flow of patients in ORION-11 is presented in Figure 14, and a summary of analysis populations (defined in Section B.2.4.3) is provided in Table 29.

Figure 14: Flow of patients (ORION-11)



Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 29: Analysis populations (ORION-11)

Analysis population	Placebo (N=807)	Inclisiran (N=810)	Total (N=1,617)
Randomised	807	810	1,617
ITT	807	810	1,617
FAS	800	803	1,603
mITT	739	724	1,463
Safety	804	811	1,615

Abbreviations: FAS, full analysis set; ITT, intention-to-treat; mITT, modified intention-to-treat.

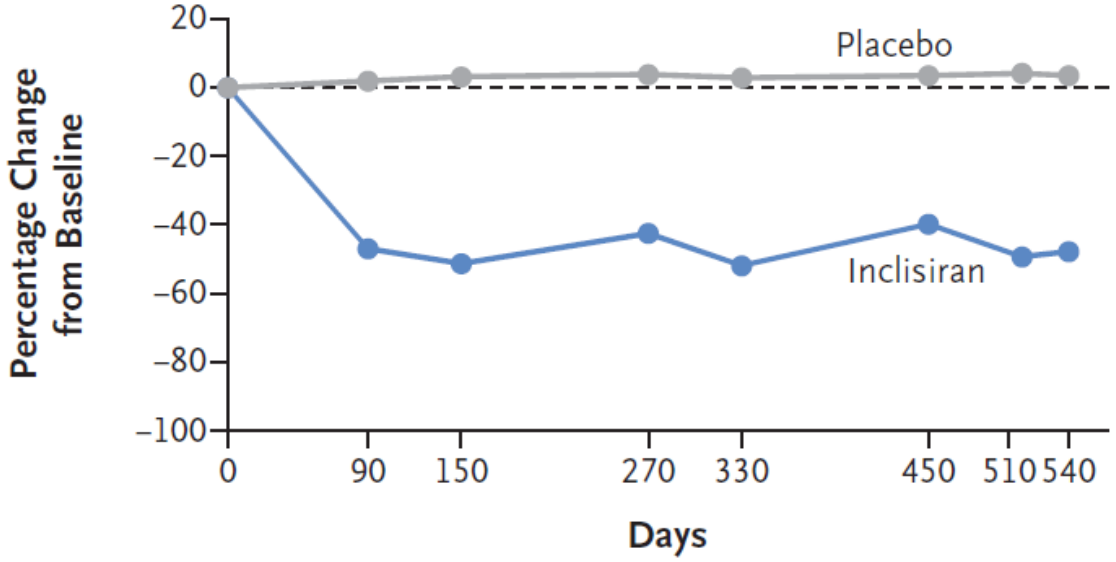
B.2.6.3.2 *Co-primary endpoints*

B.2.6.3.2.1 Percentage change in LDL-C from baseline to Day 510

The percentage change in the LDL-C level from baseline to Day 510 using a multiple imputation washout model was a decrease of 45.8% (95% CI –48.2 to –43.5) in the inclisiran group and an increase of 4.0% (95% CI 1.8 to 6.3) in the placebo group, for a between-group difference of −49.9% (95% CI −53.1 to −46.6; p<0.001).

The mean percentage change in LDL-C using least squares means is presented in Figure 15.

Figure 15: Observed mean percentage change from baseline LDL-C by visit (ITT population; ORION-11)



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

Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.3.2.2 Time-adjusted percentage change from baseline after Day 90 and up to Day 540

The time-adjusted percentage change in the LDL-C level between Day 90 and Day 540 using a control-based PMM was a decrease of 45.8% (95% CI −47.5 to −44.1) in the inclisiran group and an increase of 3.4% (95% CI 1.7 to 5.1) in the placebo group, for a between-group difference of −49.2% (95% CI −51.6 to −46.8; p<0.001).

B.2.6.3.2.3 Analysis populations

Analysis of the co-primary endpoints using the FAS and mITT populations (Section B.2.4.3) produced similar statistically significant placebo-adjusted differences (p<0.0001).

B.2.6.3.2.4 Sensitivity analyses

Three additional, pre-specified sensitivity analyses (PMM, MMRM, ANCOVA with country as a covariate) for handling missing values were performed. Similar and statistically significant (p<0.0001), placebo-adjusted differences were observed for both co-primary endpoints regardless of sensitivity analysis used to handle missing values (Table 30 and Table 31).

Table 30: Sensitivity analyses of percentage change in LDL-C from baseline to Day 510 (ITT population; ORION-11)

	Placebo (N=807)	Inclisiran (N=810)	p-value
Control-based PMM[†]			
LSM (95% CI)	4.09 (1.88, 6.31)	–47.73 (–49.93, –45.53)	
LSM difference (95% CI) from placebo		–51.82 (–54.94, –48.70)	<0.0001
MMRM[‡]			
LSM (95% CI)	3.87 (1.71, 6.03)	–48.81 (–50.98, –46.64)	
LSM difference (95% CI) from placebo		–52.68 (–55.74, –49.62)	<0.0001
ANCOVA from multiple imputation washout model including country[¶]			
LSM (95% CI)	1.93 (–1.84, 5.71)	–47.95 (–51.87, –44.02)	
LSM difference (95% CI) from placebo		–49.88 (–55.30, –44.46)	<0.0001

[†]A control-based PMM was used for missing data imputation with 100 total imputed datasets. An MMRM on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's method.
[‡]A MMRM analysis that assumes missing data are MAR was performed. The model included fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. The REML estimation approach was used with the covariance structure set as Unstructured. A linear contrast at Day 510 was used to compare treatment groups.
[¶]A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. This modified model assumed missing Day 510 MAR for inclisiran patients if they received all 4 doses and had data observed at Day 540. ANCOVA on each of the 100 datasets was performed by including fixed effects for treatment, country, interaction between treatment and country, and baseline LDL-C as a covariate. Treatment effects from the 100 analyses were combined using Rubin's Method.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intention-to-treat; LDL-

C, low-density lipoprotein cholesterol; LSM, least squares mean; MMRM, mixed-effects model for repeated measures; PMM, pattern-mixture model; REML, restricted maximum likelihood

Table 31: Sensitivity analyses of time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 (ITT population; ORION-11)

	Placebo (N=807)	Inclisiran (N=810)	p-value
MMRM[†]			
LSM (95% CI)	3.35 (1.67, 5.02)	–46.58 (–48.25, –44.90)	
LSM difference (95% CI) from placebo		–49.92 (–52.29, –47.55)	<0.0001
Control-based PMM including country[‡]			
LSM (95% CI)	4.05 (1.26, 6.83)	–47.35 (–50.20, –44.50)	
LSM difference (95% CI) from placebo		–51.39 (–55.37, –47.42)	<0.0001
Two sample t-test[¶]			
LSM (95% CI)	3.50 (1.60, 5.40)	–45.97 (–47.48, –44.47)	
LSM difference (95% CI) from placebo		–49.47 (–51.90, –47.05)	<0.0001

[†]A MMRM analysis that assumes missing data are MAR was performed. The model included fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate.
[‡]A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets.
[¶]The time-adjusted percentage change was calculated by taking the arithmetic mean of calculated percentage change in LDL-C from baseline at each visit after Day 90 through Day 540.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LSM, least squares mean; MMRM, mixed-effects model for repeated measurements; PMM, pattern-mixture model

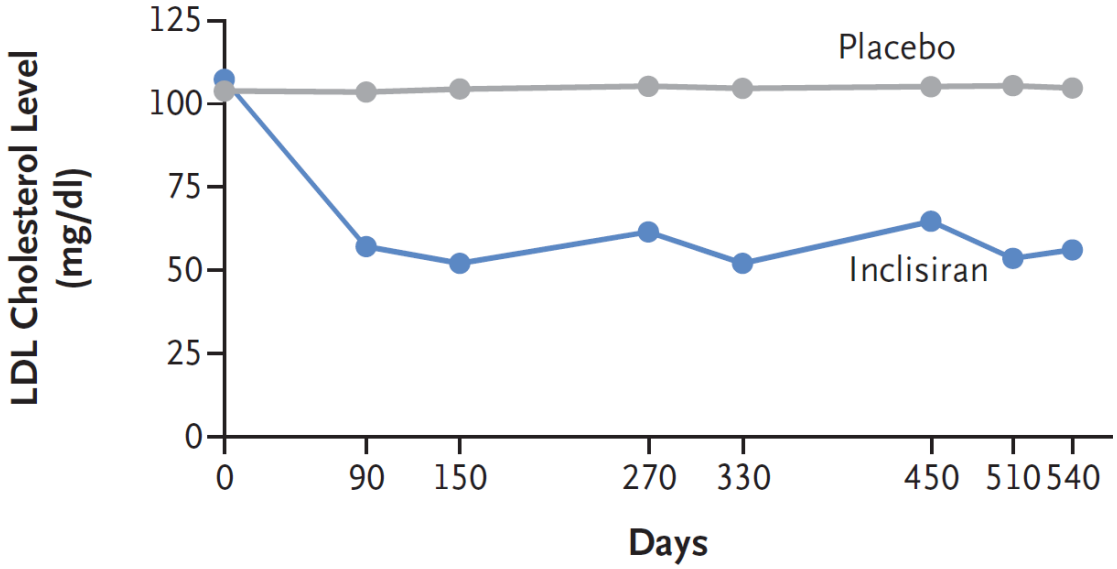
B.2.6.3.3 *Key secondary endpoints*

B.2.6.3.3.1 Absolute change in LDL-C from baseline to Day 510

The absolute change in LDL-C level at Day 510 using a control-based PMM was an increase of 0.03 mmol/l in the placebo group and a decrease of 1.32 mmol/l in the inclisiran group, for a between-group difference of −1.34 mmol/l (95% CI −1.42 to −1.26 mmol/l; p<0.001).

The absolute change in LDL-C using least squares means is presented in Figure 16.

Figure 16: Observed absolute change in LDL-C by visit (ITT population; ORION-11)



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

Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.3.3.2 Time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540

The time-adjusted absolute change in LDL-C level from Day 90 to Day 540 using a control-based PMM was an increase of 0.01 mmol/l in the placebo group and a decrease of 1.26 mmol/l in the inclisiran group, for a between-group difference of −1.26 mmol/l (95% CI, −1.33 to −1.20 mmol/l; p<0.001).

B.2.6.3.3.3 Percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B, and non-HDL-C

Significant reductions were observed in PCSK9, total cholesterol, Apo-B and non-HDL-C (p<0.0001 for all comparisons). Percentage changes calculated using a control-based PMM are shown in Table 32.

Table 32: Percentage change in PCSK9, total cholesterol, Apo-B and non-HDL-C from baseline to Day 510 (ITT population; ORION-11)

	Placebo (n=807)	Inclisiran (n=810)	p-value
PCSK9			
LSM (95% CI)	15.62 (13.72, 17.53)	–63.64 (–65.55, –61.74)	
LSM difference (95% CI) from placebo		–79.27 (–81.97, –76.57)	<0.0001
Total cholesterol			
LSM (95% CI)	1.79 (0.38, 3.21)	–28.00 (–29.40, –26.60)	
LSM difference (95% CI) from placebo		–29.79 (–31.78, –27.81)	<0.0001
Apo-B			
LSM (95% CI)	0.79 (–0.82, 2.41)	–38.15 (–39.76, –36.54)	
LSM difference (95% CI) from placebo		–38.94 (–41.21, –36.67)	<0.0001
Non-HDL-C			
LSM (95% CI)	2.15 (0.22, 4.09)	–41.16 (–43.09, –39.24)	
LSM difference (95% CI) from placebo		–43.32 (–46.04, –40.60)	<0.0001

Abbreviations: Apo-B, apolipoprotein B; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; LS, least squares; PCSK9, proprotein convertase subtilisin/kexin type 9

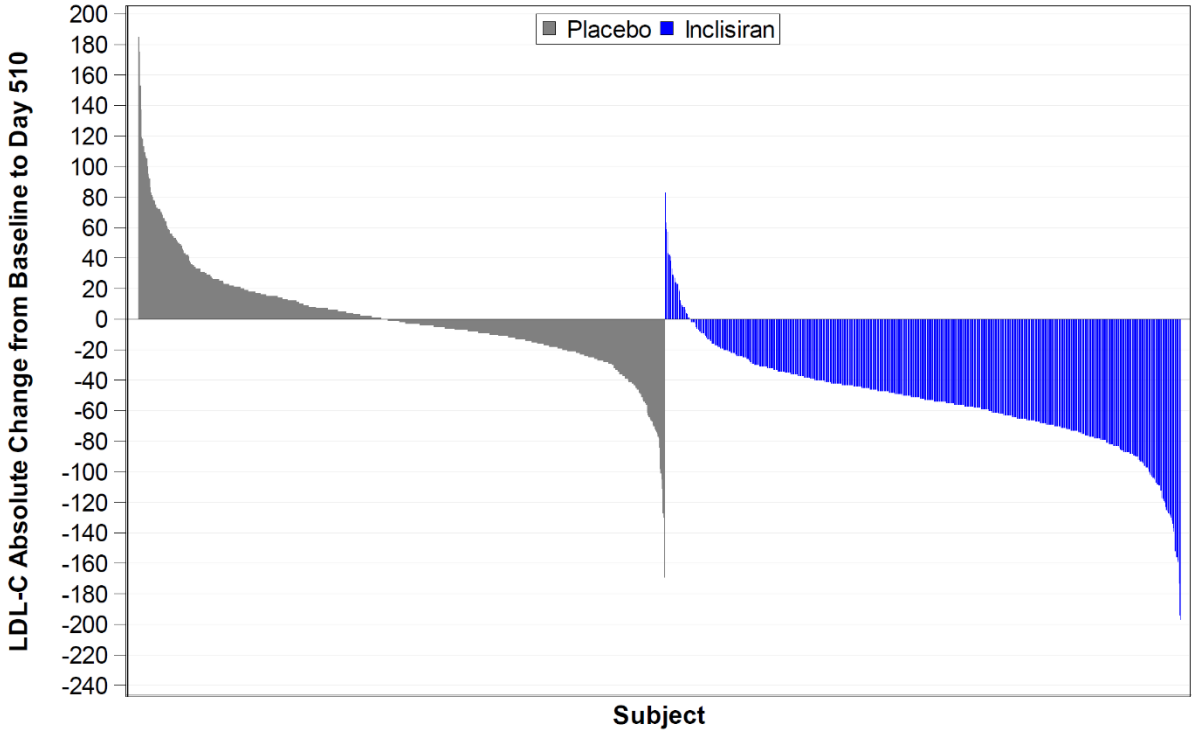
B.2.6.3.4 *Other secondary endpoints*

B.2.6.3.4.1 Absolute change and percentage change in LDL-C from baseline to each assessment time up to Day 540

The placebo-adjusted percentage reduction in LDL-C from baseline ranged between 42.5% and 54.2% at all time points up to Day 540 (observed values, p<0.0001 for all time points). The results were similar regardless of analysis population (ITT, FAS, mITT).

A waterfall plot of absolute change in LDL-C from baseline to Day 510 is provided in Figure 17.

Figure 17: Waterfall plot of absolute change in LDL-C from baseline to Day 510 (ITT population; ORION-11)



Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.3.4.2 Absolute change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B and non-HDL-C

The placebo-adjusted change in PCSK9, total cholesterol, Apo-B and non-HDL-C from baseline to Day 510 were all statistically significant (p<0.0001) (Table 33) The results were similar regardless of analysis population used (ITT, FAS, mITT).

Table 33: Absolute change from baseline to Day 510 in PCSK9, total cholesterol, apo-b and non-HDL-C using ANCOVA† (ITT population; ORION-11)

	Placebo (N=807)	Inclisiran (N=810)	p-value
PCSK9 (ug/L)			
LSM (95% CI)	40.71 (34.94, 46.47)	–245.1 (–250.9, –239.2)	
LSM difference (95% CI) from placebo		–285.8 (–294.0, –277.6)	<0.0001
Total cholesterol (mg/dl)			
LSM (95% CI)	0.31 (–2.25, 2.88)	–54.90 (–57.49, –52.31)	
LSM difference (95% CI) from placebo		–55.21 (–58.86, –51.56)	<0.0001

	Placebo (N=807)	Inclisiran (N=810)	p-value
Apolipoprotein B (mg/dl)			
LSM (95% CI)	–1.24 (–2.72, 0.25)	–38.89 (–40.39, –37.39)	
LSM difference (95% CI) from placebo		–37.66 (–39.77, –35.54)	<0.0001
Non-HDL cholesterol calculated (mg/dl)			
LSM (95% CI)	–0.53 (–3.05, 2.00)	–58.77 (–61.32, –56.23)	
LSM difference (95% CI) from placebo		–58.25 (–61.83, –54.66)	<0.0001

†ANCOVA including fixed effects for treatment and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HDL, high density lipoprotein; ITT, intention-to-treat; LS, least squares; PCSK9; proprotein convertase subtilisin/kexin type 9.

B.2.6.3.4.3 Individual responsiveness defined as the number of patients reaching on-treatment LDL-C levels of <25 mg/dl, <50 mg/dl, <70 mg/dl, and <100 mg/dl at Day 510

At Day 510, 81.6% (661/810) of inclisiran-treated patients reached an LDL-C level of <100 mg/dl compared with 52.7% (425/807) of placebo-treated patients. The number of patients achieving defined threshold levels is presented in Table 34.

Table 34: Individual responsiveness as measured by LDL-C levels at day 510† (ITT population; ORION-11)

LDL-C (mg/dl) levels	Placebo (N=807) (%)	Inclisiran (N=810) (%)
<25 mg/dl	1 (0.1)	95 (11.7)
<50 mg/dl	19 (2.4)	420 (51.9)
<70 mg/dl	104 (12.9)	564 (69.6)
<100 mg/dl	425 (52.7)	661 (81.6)
≥100 mg/dl	314 (38.9)	63 (7.8)
Missing	68 (8.4)	86 (10.6)

†Patients can be counted in multiple categories.
Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.3.4.4 Proportion of patients in each group with greater or equal to 50% LDL-C reduction from baseline

At any time during the study, 81.9% (658/803) of inclisiran-treated patients had ≥50% LDL-C reduction from baseline compared with 5.9% (47/800) of placebo-treated patients (Table 35).

Table 35: Proportion of patients in each group with greater or equal to 50% LDL-C reduction from baseline (ITT Population; ORION-11)

LDL-C (mg/dl) levels	Placebo (N=807) n/N (%)	Inclisiran (N=810) n/N (%)
Number of patients reaching LDL-C level ≥50%		
Reduction from baseline at any visit	47/800 (5.9)	658/803 (81.9)
Number of patients reaching LDL-C level ≥50%		
Reduction from baseline at[†]:		
Visit 3 Day 90	10/797 (1.3)	413/790 (52.3)
Visit 4 Day 150	13/785 (1.7)	491/796 (61.7)
Visit 5 Day 270	12/774 (1.6)	338/778 (43.4)
Visit 6 Day 330	18/773 (2.3)	471/773 (60.9)
Visit 7 Day 450	21/764 (2.7)	301/768 (39.2)
Visit 8 Day 510	17/739 (2.3)	418/724 (57.7)
Visit 9 Day 540	19/749 (2.5)	420/742 (56.6)

[†]Only patients with LDL-C values at a given visit are included in that visit.
Abbreviations: ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol.

B.2.6.3.4.5 Proportion of patients in each group who attain global lipid targets for their level of ASCVD risk

At any visit, 92.4% (741/802) of inclisiran-treated patients achieved their corresponding LDL-C targets compared with 41.9% (335/800) of placebo-treated patients. At Day 510, 81.7% (522/639) of inclisiran-treated patients with ASCVD achieved their LDL-C target of <70 mg/dl compared with 16.0% (103/644) of placebo-treated patients with ASCVD. At Day 510, 77.6% (66/85) of inclisiran-treated patients with ASCVD risk-equivalent achieved their LDL-C target of <100 mg/dl compared with 30.5% (29/95) of placebo-treated ASCVD risk-equivalent patients. Similar results were observed at all other time points.

B.2.6.3.4.6 Absolute change and percentage change in lipoprotein-a from baseline to Day 540

Inclisiran lowered lipoprotein-a levels from baseline through Day 540 (Table 36).

Table 36: Absolute and percentage change from baseline to Day 540 in lipoprotein-a using MMRM† (ITT population; ORION-11)

	Placebo (N=807)	Inclisiran (N=810)	p-value
Absolute change (nmol/L)			
LSM (95% CI)	-2.4 (-6.7, 1.9)	-17.2 (-21.4, -12.9)	
LSM difference (95% CI) from placebo		-14.8 (-18.3, -11.2)	<.0001
Percentage change (%)			
LSM (95% CI)	9.2 (3.8, 14.5)	-9.9 (-15.2, -4.6)	
LSM difference (95% CI) from placebo		-19.1 (-23.6, -14.6)	<.0001

†MMRM including fixed effects for treatment, visit, interaction between treatment and visit, current use of statins or other lipid lowering therapies (yes/no), and baseline LDL-C as a covariate.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LSM, least squares mean; MMRM, mixed-effect models for repeated measures.

B.2.6.3.4.7 Absolute change and percentage change in other lipids, apolipoproteins, and PCSK9 from baseline at each subsequent visit to Day 540

Inclisiran lowered PCSK9 levels from baseline through Day 540. In addition, changes in apolipoprotein A1, apolipoprotein B, total cholesterol, C-reactive protein, HDL cholesterol, non-HDL cholesterol, triglycerides, VLDL cholesterol, and VLDL cholesterol were consistent with the changes observed in LDL-C and PCSK9. These observations were similar regardless of analysis population used (ITT, FAS, mITT).

B.2.6.3.4.8 Maximum percentage change in LDL-C

The placebo-adjusted mean maximum (based on individual patient's maximum reduction) percent change in LDL-C from baseline was 68.7% (p<0.0001). The results were statistically significant (p<0.0001) and similar regardless of analysis population used (ITT, FAS, mITT).

B.2.6.3.5 *Exploratory endpoints*

B.2.6.3.5.1 MACE defined as the composite of CV death, resuscitated cardiac arrest, non-fatal MI, and stroke (ischemic or haemorrhagic) using a pre-defined MedDRA search to identify events.

The proportion of patients with a MACE event was 10.3% (83/804) in placebo-treated patients compared with 7.8% (63/811) in inclisiran-treated patients.

B.2.6.3.5.2 Proportion of patients in each group with any LDL-C reduction from baseline at any visit (responders).

All but five patients (99.4%; 797/802) responded to inclisiran by having a reduction in LDL-C at any time during study. Two of the five non-responders reduced or discontinued statin therapy during the study, four of the five had post-baseline PCSK9 reductions, and one of the five had no post-baseline PSCK9 values measured.

B.2.7 Subgroup analysis

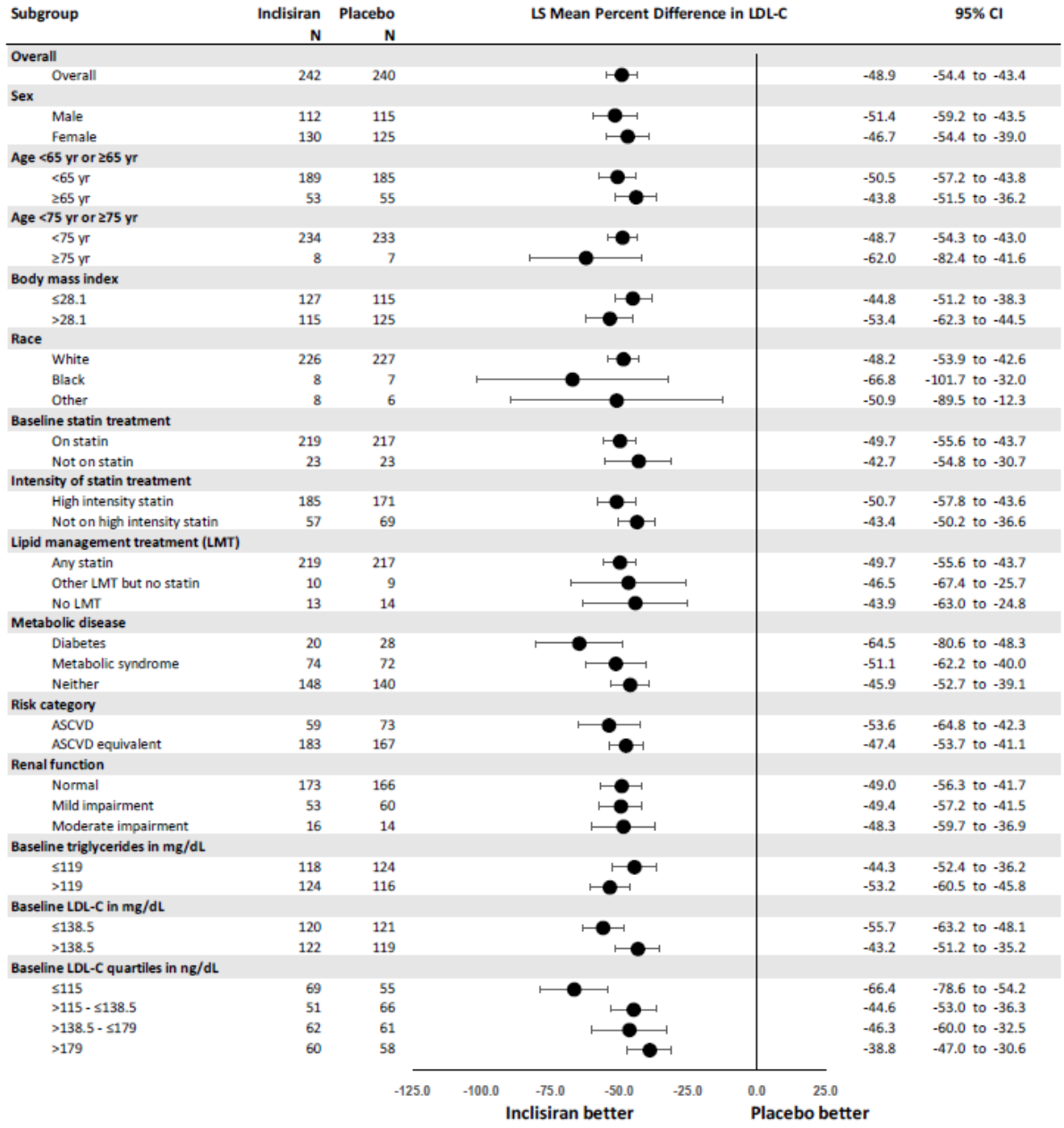
B.2.7.1 Mean percentage change in LDL-C from baseline to day 510

Subgroup analysis for treatment differences in percentage change in LDL-C from baseline to day 510 for ORION-9, 10 and 11, using the MMRM method, are illustrated in Figure 18 to Figure 20 (102-104). Except for baseline LDL-C in the ASCVD population, there were no statistically significant differences between subgroups across the ORION trial populations. ASCVD populations defined by baseline LDL-C (>95 mg/dL in ORION-10 and >97 mg/dL in ORION-11) showed different treatment effects between subgroups.

Additional analyses demonstrated that the decreasing percentage change observed as baseline LDL-C values increase is driven by changes in the placebo arm. This effect was also observed for comparator therapies (77). Feedback from UK clinical experts at a recent Novartis advisory board concluded that though there is no clear reason for this increase, a possible explanation could be that these patient with lower

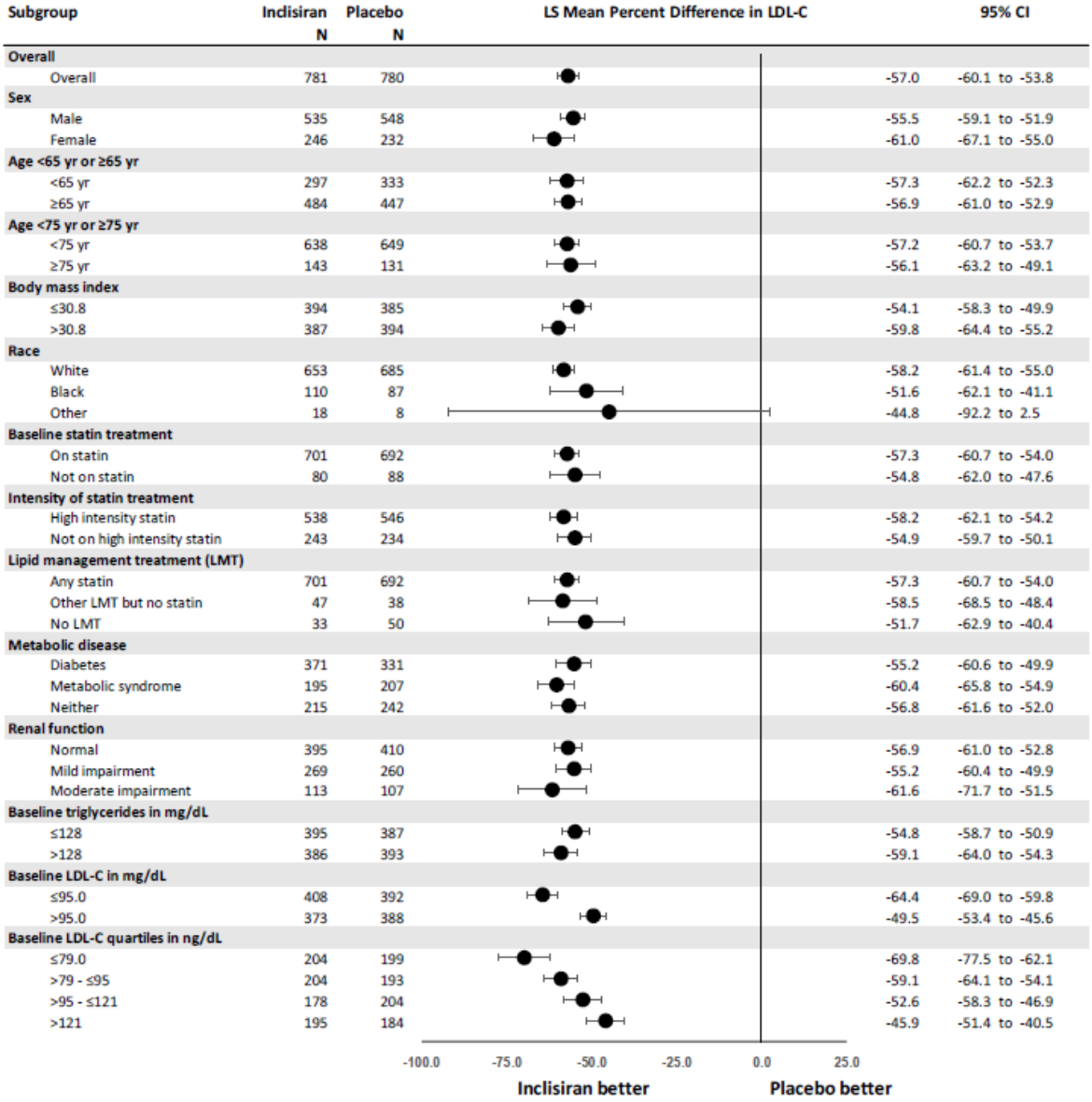
LDL-C levels are not very strict with medication. However, it was recommended that there should be no adjustment for this effect in the placebo arm (20).

Figure 18: Forest plot for subgroup analysis for differences in percentage change in LDL-C from baseline to day 510 in ORION-9 (MMRM)



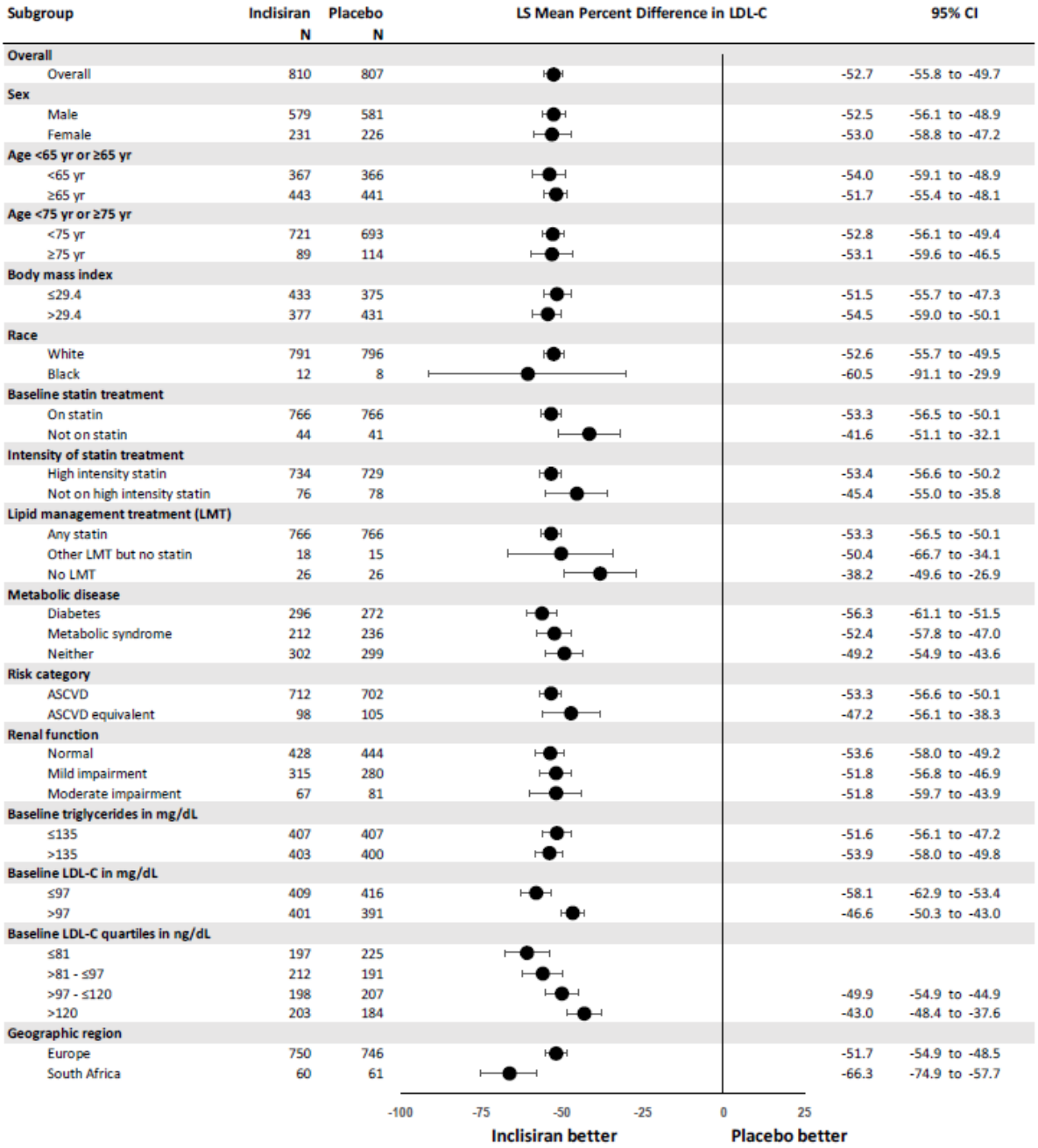
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; MMRM, mixed-effects model with repeated measures.

Figure 19: Forest plot for subgroup analysis for differences in percentage change in LDL-C from baseline to day 510 in ORION-10 (MMRM)



Abbreviations: CI, confidence interval; LDL-C, low density lipoprotein cholesterol; MMRM, mixed-effects model with repeated measures.

Figure 20: Forest plot for subgroup analysis for differences in percentage change in LDL-C from baseline to day 510 in ORION-11 (MMRM)



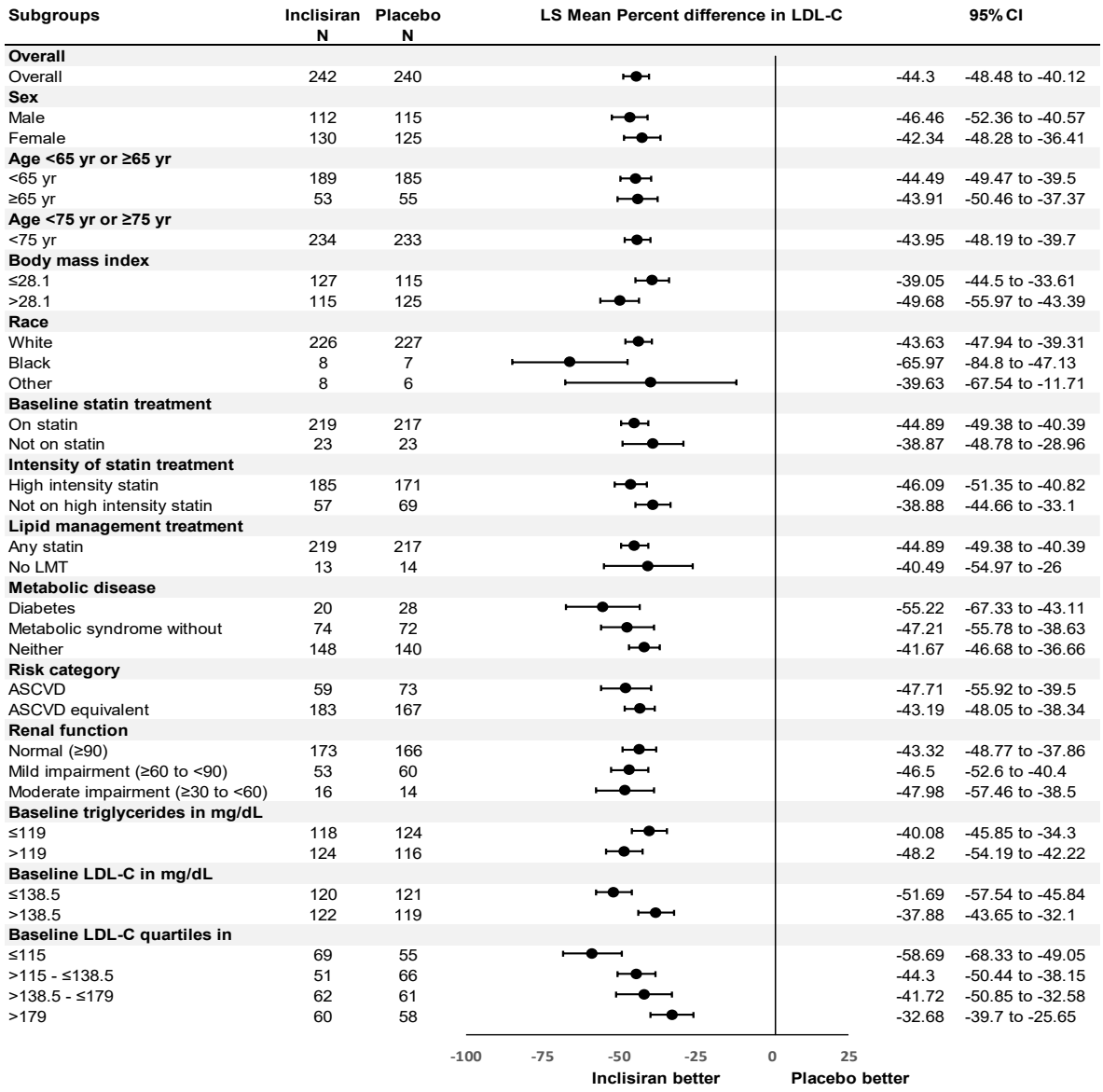
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; MMRM, mixed-effects model with repeated measures.

B.2.7.2 Time-adjusted percentage change from baseline in LDL-C after Day 90 and up to Day 540

Subgroup analysis for treatment differences in time adjusted LDL-C between day 90 and day 540 for ORION-9, 10 and 11 are illustrated in Figure 21–Figure 23 using the control based pattern mixture model (PMM) method (105). There were no statistically significant differences between the majority of subgroups across the ORION trial

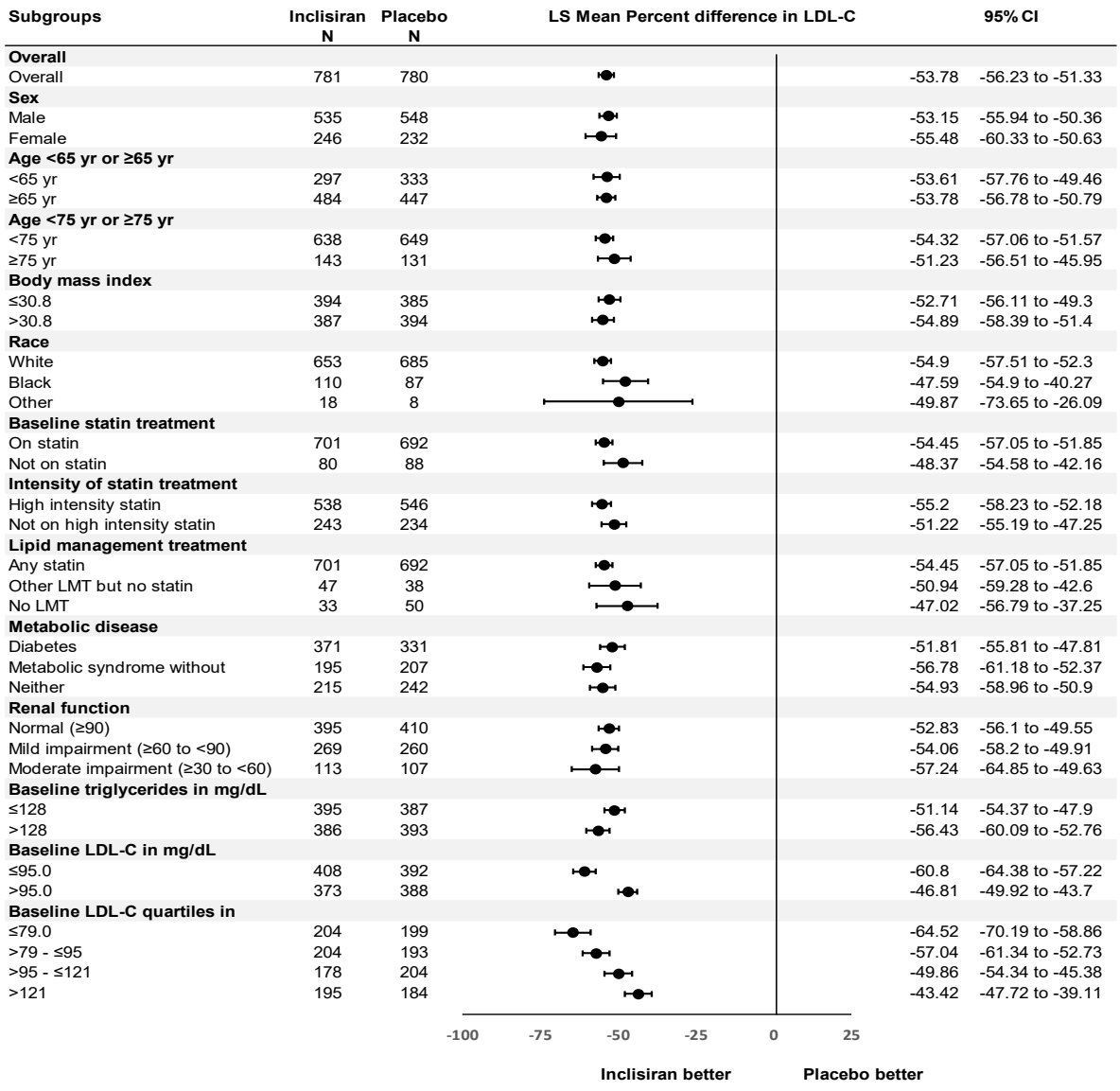
populations. ASCVD populations defined by baseline LDL-C (>95 mg/dL in ORION-10 and >97 mg/dL in ORION-11) showed different treatment effects between subgroups. In ORION-11 there was a difference in treatment effect between patients who were on statin at baseline and patients who were not.

Figure 21: Forest plot for subgroup analysis for differences in time adjusted LDL-C between day 90 and day 540 in ORION-9 (control-based PMM)



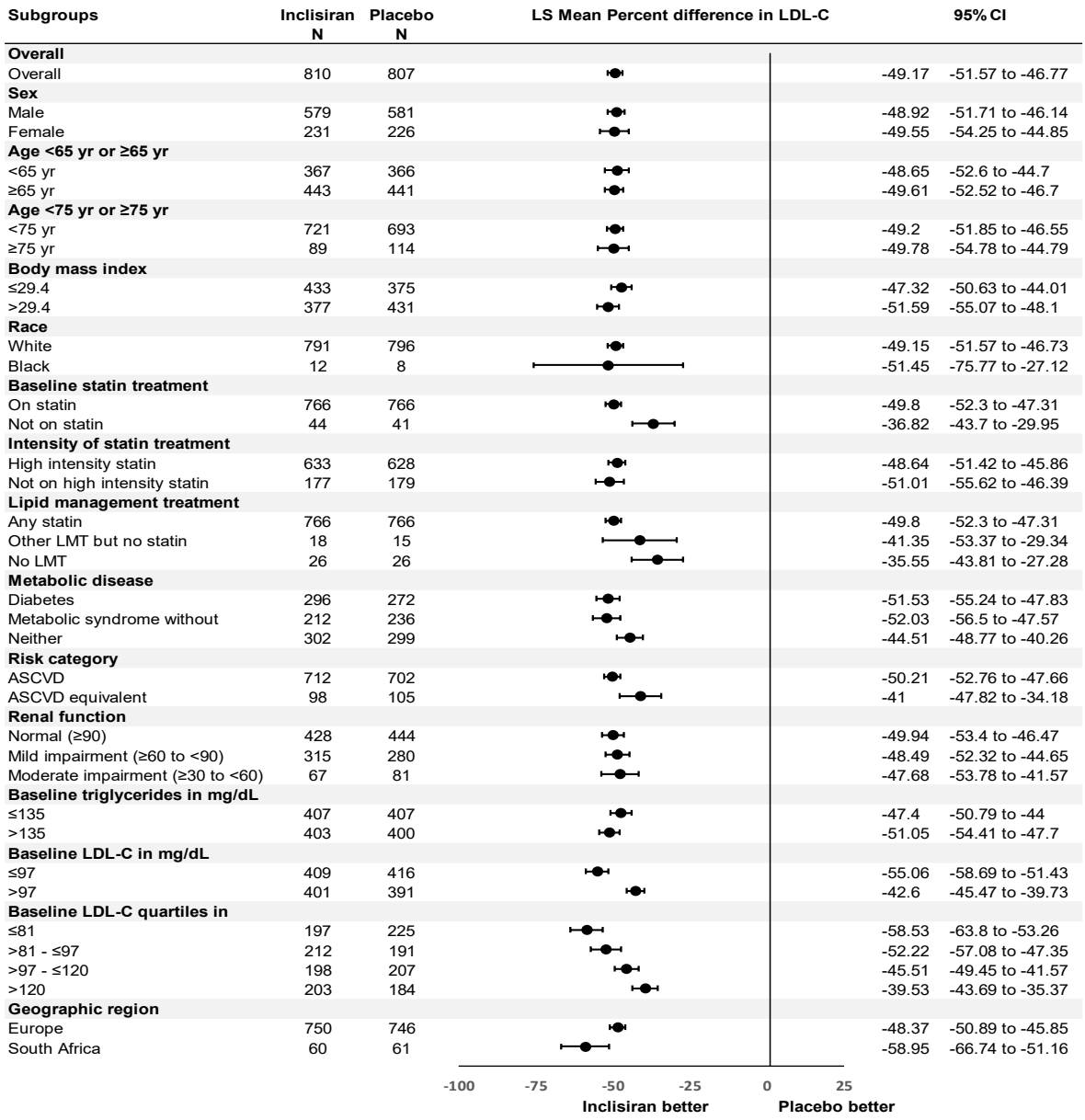
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering therapy; PMM, pattern mixture model.

Figure 22: Forest plot for subgroup analysis for differences in time adjusted LDL-C between day 90 and day 540 in ORION-10 (control-based PMM)



Abbreviations: CI, confidence interval; LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering therapy; PMM, pattern mixture model.

Figure 23 Forest plot for subgroup analysis for differences in time adjusted LDL-C between day 90 and day 540 in ORION-11 (control-based PMM)



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering therapy; PMM, pattern mixture model.

B.2.8 Meta-analysis

Given the near-identical methodology of the ORION-10 and -11 trials which enrolled patients with ASCVD or ASCVD-RE (in ORION-11 only; termed PPER within this submission) (Section B.2.3), data from the studies were pooled. As shown in Section B.2.3.6, patient demographics and baseline LDL-C levels were similar between the studies.

[redacted]

Table 37: Subject disposition within the pooled efficacy dataset, ITT population

Category	Placebo (N=1,587) n (%)	Inclisiran (N=1,591) n (%)
Completers*	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Death	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
PCSK9 initiation**	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing reason	[redacted]	[redacted]

*A completer is defined as completing the Day 540 visit.
**PCSK9 initiation is defined as the initiation of protocol-prohibited approved PCSK9 inhibitor
Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9.

B.2.8.1 Mean percentage change in LDL-C from baseline to Day 510

[redacted]

Table 38: Change from baseline in LDL-C to Day 510 in pooled efficacy dataset, ITT population

	Placebo (N=1591)	Inclisiran (N=1587)	p-value
% CFB in LDL-C to Day 510, observed values			
LSM (95% CI)	[redacted]	[redacted]	
LSM difference (95% CI) from placebo		[redacted]	[redacted]
% CFB in LDL-C to Day 510, washout-imputed values			
LSM (95% CI)	[redacted]	[redacted]	
LSM difference (95% CI) from placebo		[redacted]	[redacted]

Abbreviations: CFB, change from baseline; CI, confidence interval; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LSM, least squares mean.

Figure 24: Percentage change from baseline in LDL-C (mg/dl) by visit in pooled efficacy dataset, ITT population

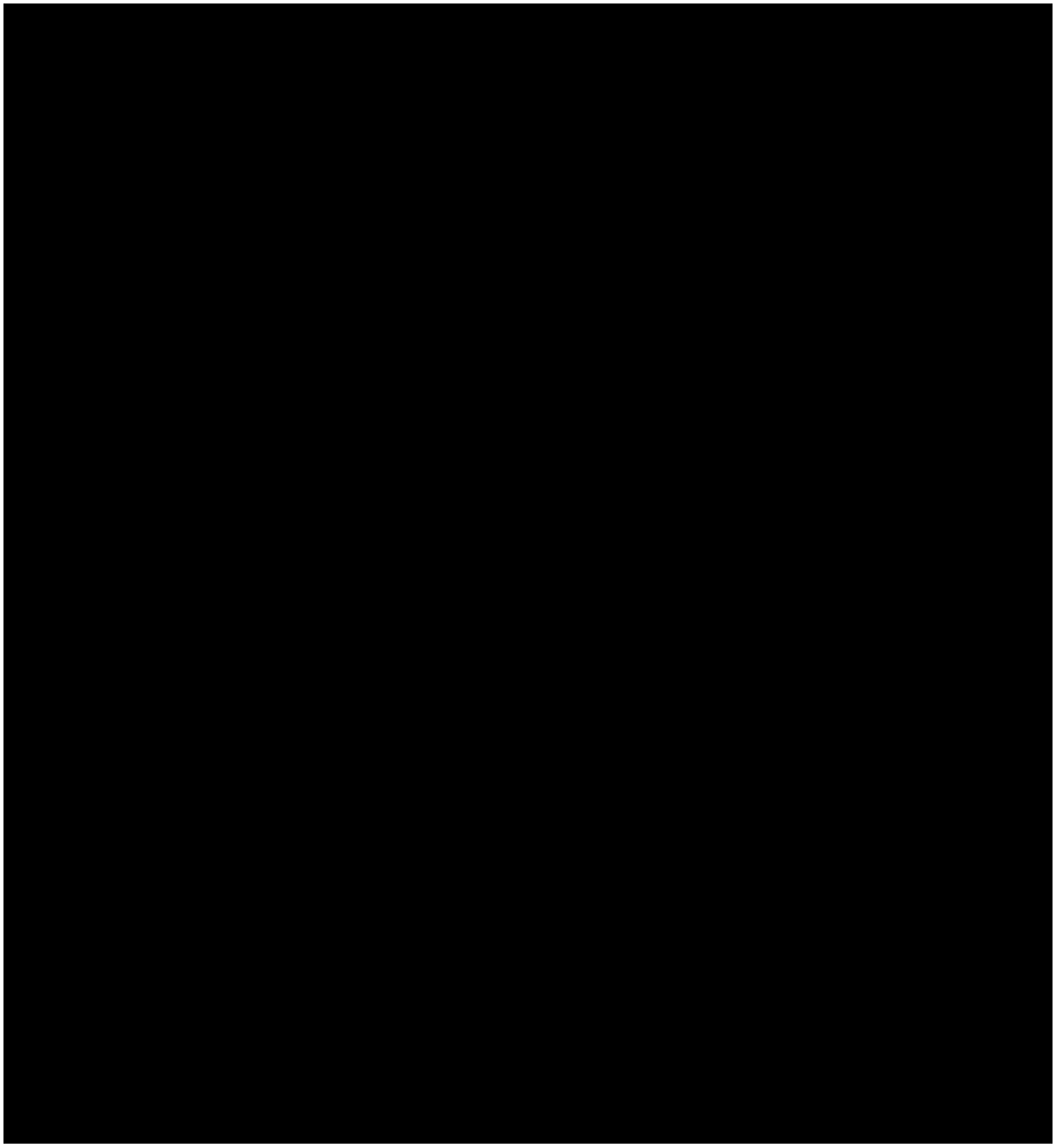
[redacted]

Abbreviations: ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol.

Subgroup analysis for treatment differences in percentage change in LDL-C from baseline to day 510 within the pooled efficacy dataset using the MMRM method are illustrated in Figure 25. There were no statistically significant differences for change in LDL-C from baseline to day 510 between subgroups across the pooled efficacy dataset, except for the subgroup defined by baseline LDL-C at a 96 mg/dL threshold.

Figure 25: Forest plot for subgroup analysis for differences in percentage change in LDL-C from baseline to day 510 in pooled efficacy dataset (MMRM)

[redacted]



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; MMRM, mixed-effects model with repeated measures.

B.2.8.2 Time-adjusted percentage change from baseline in LDL-C after Day 90 and up to Day 540

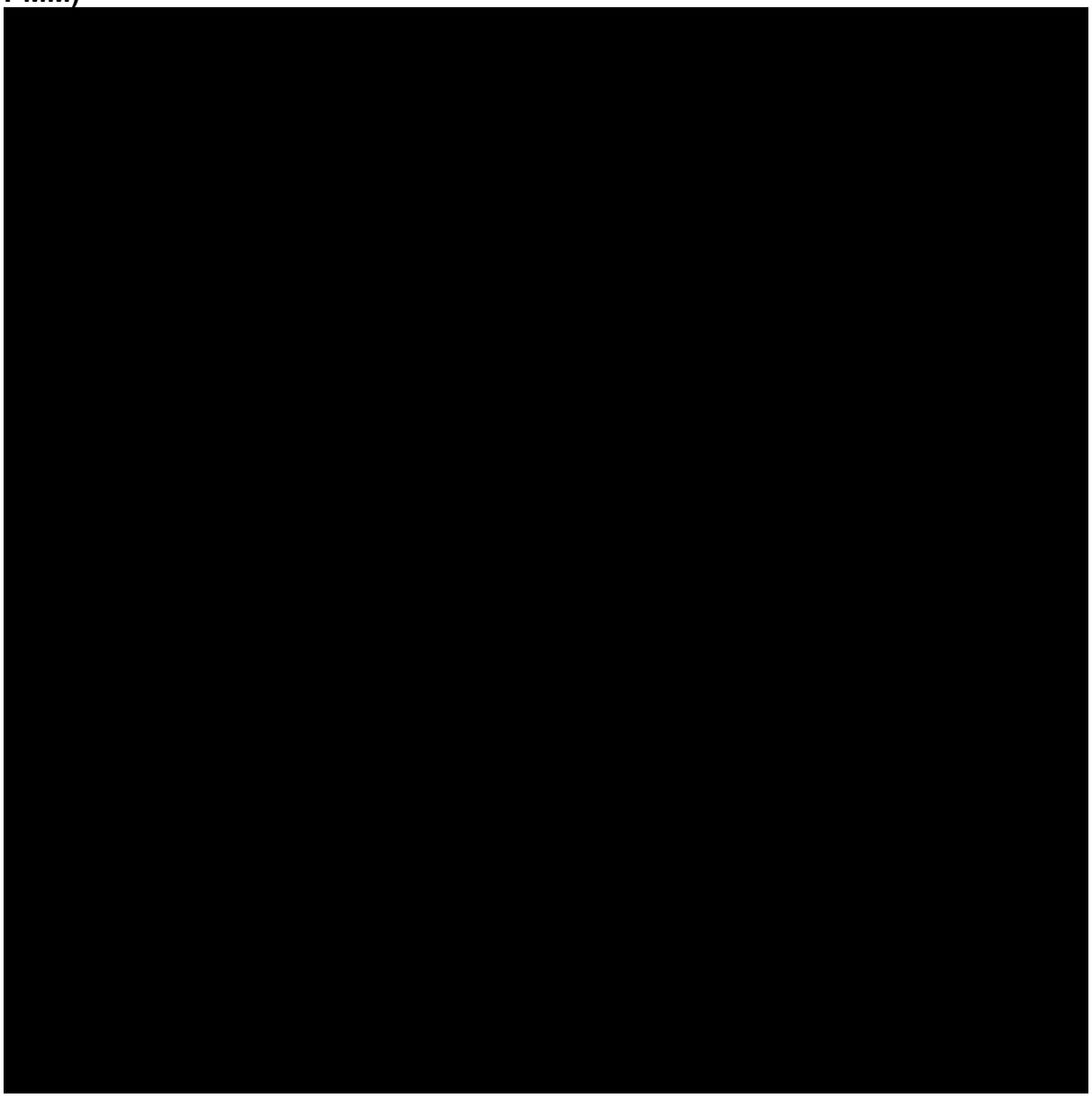
Table 39: Time-adjusted percentage change from baseline in LDL-C after Day 90 and up to Day 540 in pooled efficacy dataset, ITT population

	Placebo (N=1591)	Inclisiran (N=1587)	p-value
LSM (95% CI)	[redacted]	[redacted]	
LSM difference (95% CI) from placebo		[redacted]	[redacted]

A control-based pattern-mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and study, and baseline LDL-C as a covariate. A linear combination of the estimated means after Day 90 and up to Day 540 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's method.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LSM, least squares mean.

Subgroup analysis for treatment differences in time-adjusted change in LDL-C between Day 90 and Day 540 for the pooled efficacy dataset using the MMRM method are illustrated in Figure 26. There were no statistically significant differences for change in LDL-C from baseline to day 510 between the majority of the subgroups. Treatment effect differences were statistically significant for subgroups defined by baseline statin treatment status and baseline LDL-C level at a 96 mg/dL threshold.

Figure 26: Forest plot for subgroup analysis for differences in time adjusted LDL-C between day 90 and day 540 in pooled efficacy dataset (control-based PMM)



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering therapy; PMM, pattern mixture model.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 NMA methodology

[redacted]

Table 40: Eligible populations, comparators, and outcomes

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	• [redacted]	• [redacted]
	[redacted]	• [redacted]	
[redacted]	[redacted]	• [redacted]	
	[redacted]	• [redacted]	

[redacted]

Abbreviations: AE, adverse event; ASCVD, atherosclerotic cardiovascular disease; CFB, change from baseline; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-[redacted]

[redacted]

[redacted]

Table 41: Analyses by population and outcome

[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]	
		[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]			

Abbreviations: AE, adverse event; ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose; OD, once daily; Q2W, every two weeks; SA, sensitivity analysis; SC, subcutaneous

[redacted]

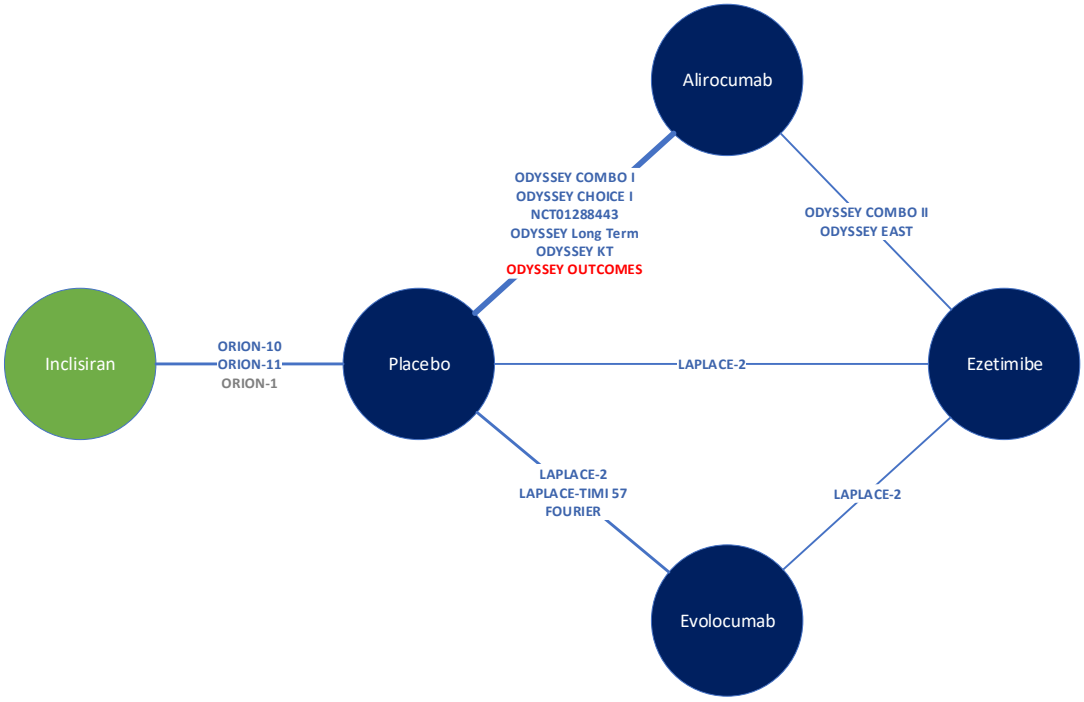
B.2.9.2 NMA results

B.2.9.2.1 *Feasibility assessment*

The feasibility assessment suggested that NMAs were not feasible for all populations and comparators of interest. Specifically, it was found that no comparator studies reported outcomes of interest for the HeFH statin intolerant population. As a result, NMAs were only feasible for patients with HeFH treated with maximally tolerated dose (MTD) statins.

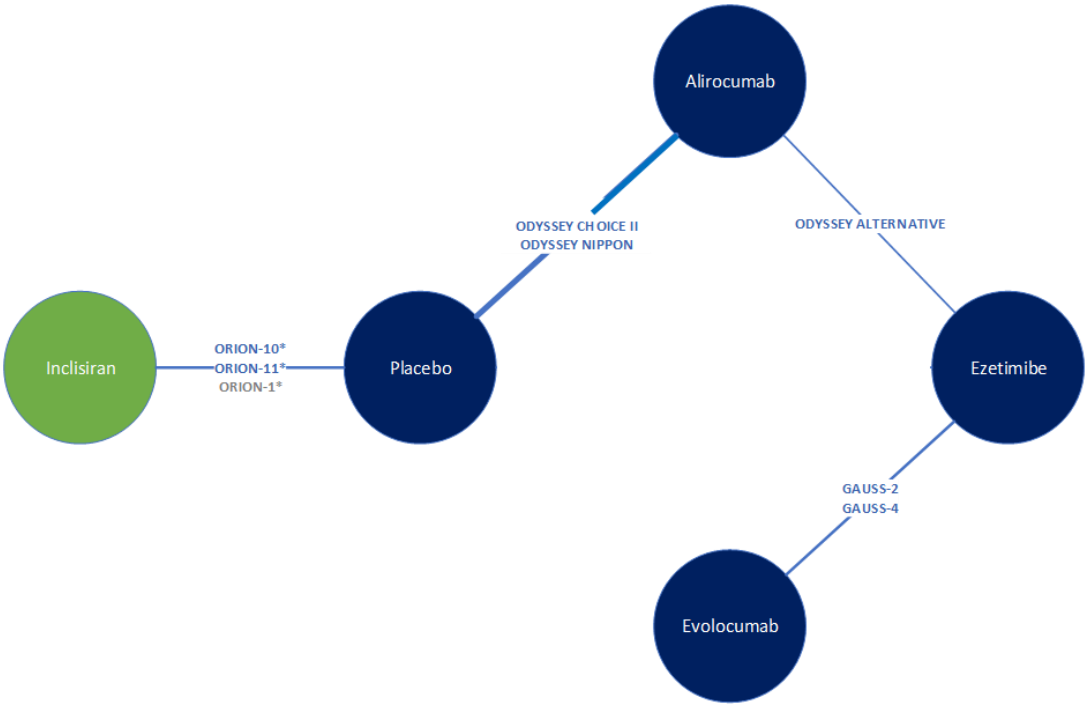
Treatment network diagrams are presented in Figure 27 to Figure 29.

Figure 27: Network diagram for ASCVD and ASCVD PPER on MTD statin



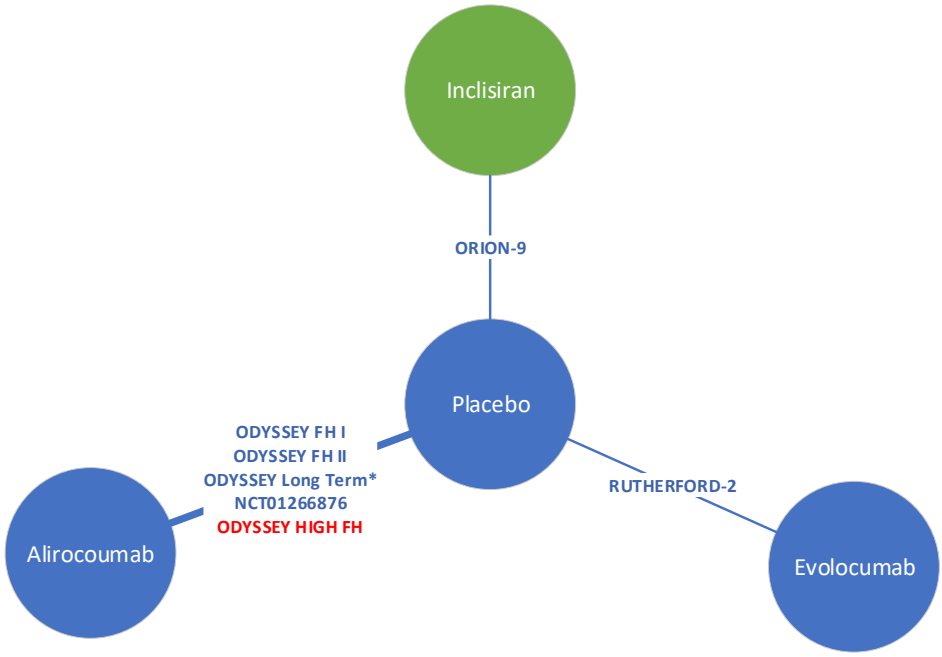
Note: Interventions and placebo arms are in addition to background statin with or without other lipid-lowering therapy (LLT).
Red text: excluded in a sensitivity analysis (SA). Grey text: only included in a SA.
Abbreviations: MTD, maximally tolerated dose.

Figure 28: Network diagram for ASCVD and ASCVD PPER intolerant to statins



* Subgroup data for statin intolerant patients to be used in the analysis
Note: Interventions and placebo arms are in addition to background statin with or without other LLT
Grey text = only included in a SA.

Figure 29: Network diagram for HeFH population



*Subgroup data for patients with HeFH were used in the analysis.
Note: Interventions and placebo arms are in addition to background statin with or without other lipid-lowering therapy (LLT); no network is feasible for statin intolerant patients.
Red text: excluded from sensitivity analysis (SA).
Abbreviations: HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose.

B.2.9.2.2 *ASCVD and PPER on MTD statins*

B.2.9.2.2.1 Percent Change in LDL-C at 24 Weeks

Base case and all SAs were conducted for percent change in LDL-C.

B.2.9.2.2.1.1 ***Base case***

[redacted]

Figure 30: ASCVD MTD: Difference in percent change in LDL-C – random effects – inclisiran versus other treatments

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose.

Figure 31: ASCVD MTD: Difference in percent change in LDL-C – random effects – treatments versus placebo

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose; NMA, network meta-analysis

B.2.9.2.2.1.2 ***Sensitivity Analyses***

[redacted]

Table 42: ASCVD MTD: SA Results for Difference in Percent Change in LDL-C – random effects – Inclisiran versus Other Treatments

Comparator	Differences in Percent CFB (95% CrI)	Probability Inclisiran is Better
[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]
[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]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; CrI, credible interval.

B.2.9.2.2.2 Absolute Change in LDL-C at 24 Weeks

[redacted]

B.2.9.2.2.2.1 ***Base Case***

[redacted]

Figure 32: ASCVD MTD: Difference in Absolute Change in LDL-C – random effects – Inclisiran versus Other Treatments

[redacted]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose

Figure 33: ASCVD MTD: Difference in Absolute Change in LDL-C – random effects – Treatments versus Placebo

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose

B.2.9.2.2.2.2 ***Sensitivity Analyses***

Table 43: ASCVD MTD: SA Results for Difference in Absolute Change in LDL-C – random effects – Inclisiran versus Other Treatments

Comparator	Difference in Absolute CFB (95% CrI)	Probability Inclisiran is Better
[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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; CrI, credible interval.

B.2.9.2.2.3 Total Discontinuations at ≥24 Weeks

[redacted]

Figure 34: ASCVD MTD: Difference in Total Discontinuations – random effects – Inclisiran versus Other Treatments

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; MTD, maximally tolerated dose.

Figure 35: ASCVD MTD: Difference in Total Discontinuations – random effects – Treatments versus Placebo

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; MTD, maximally tolerated dose.

B.2.9.2.2.4 Discontinuation Due to AEs at ≥24 Weeks

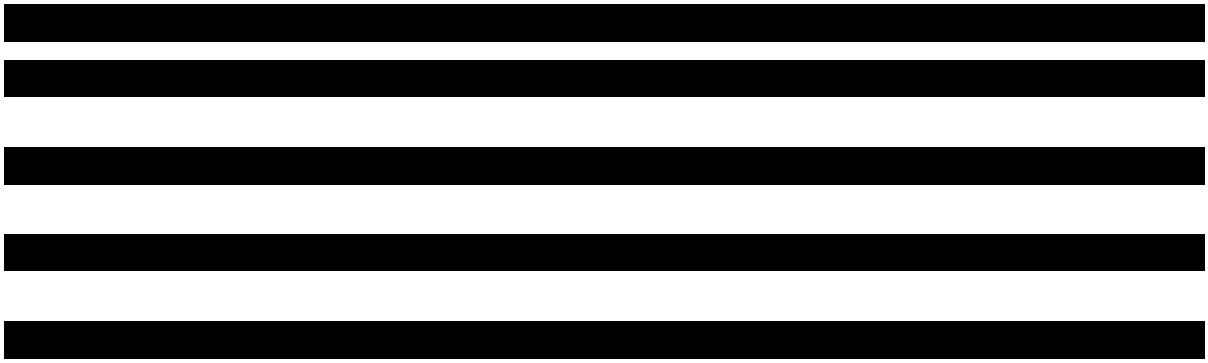
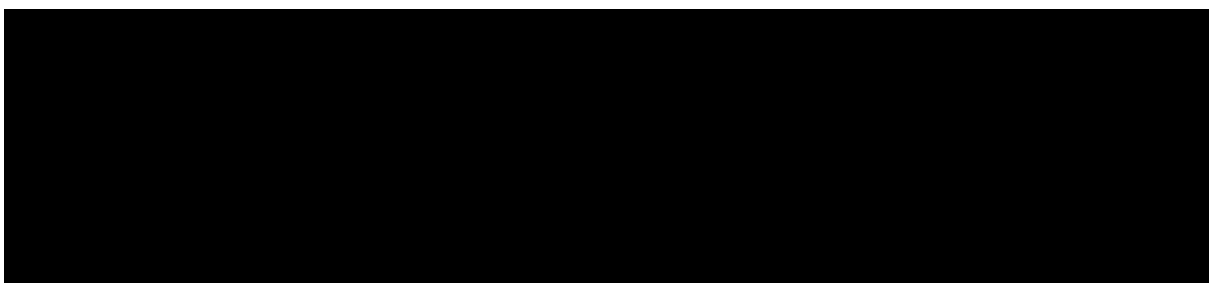


Figure 36: ASCVD MTD: Difference in Discontinuations due to AEs – random effects – Inclisiran versus Other Treatments



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; MTD, maximally tolerated dose.

Figure 37: ASCVD MTD: Difference in Discontinuations due to AEs – random effects – Treatments versus Placebo

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; MTD, maximally tolerated dose.

B.2.9.2.2.5 Percent Change in HDL-C at 24 Weeks

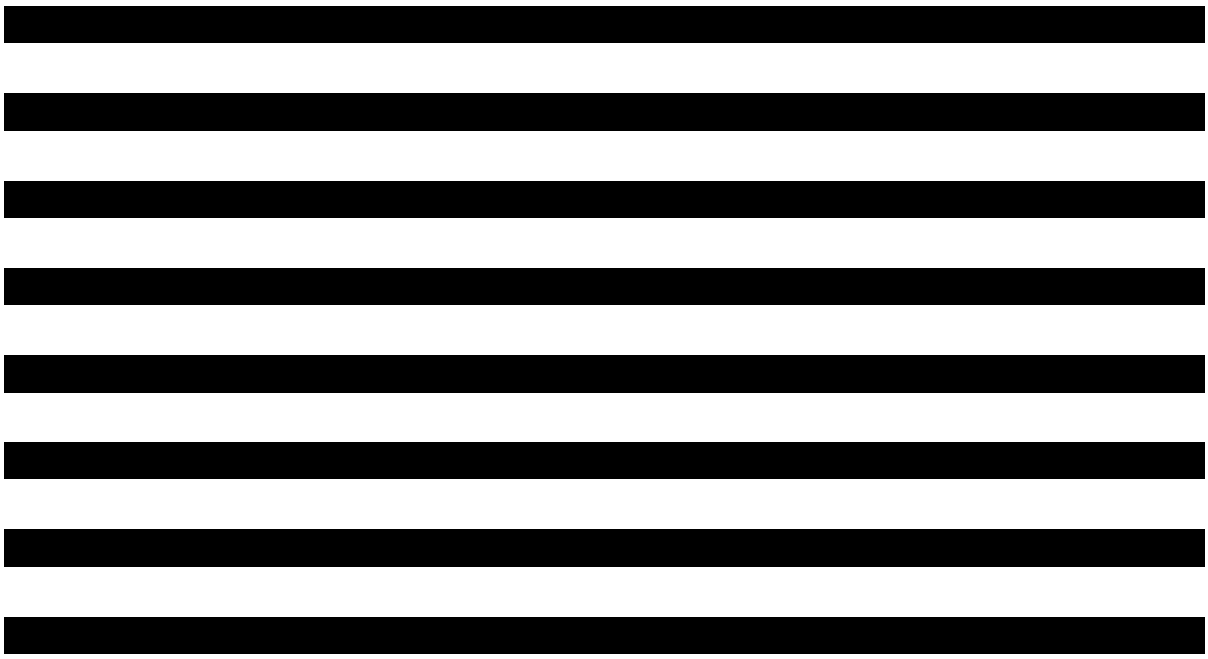


Figure 38: ASCVD MTD: Difference in Percent Change in HDL-C – random effects – Inclisiran versus Other Treatments

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; Crl, credible interval.

Figure 39: ASCVD MTD: Difference in Percent Change in HDL-C – random effects – Treatments versus Placebo

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; Crl, credible interval.

B.2.9.2.3 *ASCVD and ASCVD PPER Intolerant to Statins*

B.2.9.2.3.1 Percent Change in LDL-C at 24 Weeks

B.2.9.2.3.1.1 ***Base Case***

[redacted]

Figure 40: ASCVD Intolerant: Difference in Percent Change in LDL-C – random effects – Inclisiran versus Other Treatments

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL- C, low-density lipoprotein cholesterol.

Figure 41: ASCVD Intolerant: Difference in Percent Change in LDL-C – random effects – Treatments versus Placebo

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL- C, low-density lipoprotein cholesterol; NMA, network meta-analysis.

B.2.9.2.3.1.2 *Sensitivity Analyses*

[redacted]

[redacted]

[redacted]

[redacted]

Table 44: ASCVD Intolerant: SA Results for Difference in Percent Change in LDL-C – random effects – Inclisiran versus Other Treatments

Comparator	Difference in Percent CFB (95% CrI)	Probability Inclisiran is Better
[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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; CrI, credible interval.

B.2.9.2.3.2 Absolute Change in LDL-C at 24 Weeks

[redacted]

[redacted]

[redacted]

B.2.9.2.3.2.1 *Base Case*

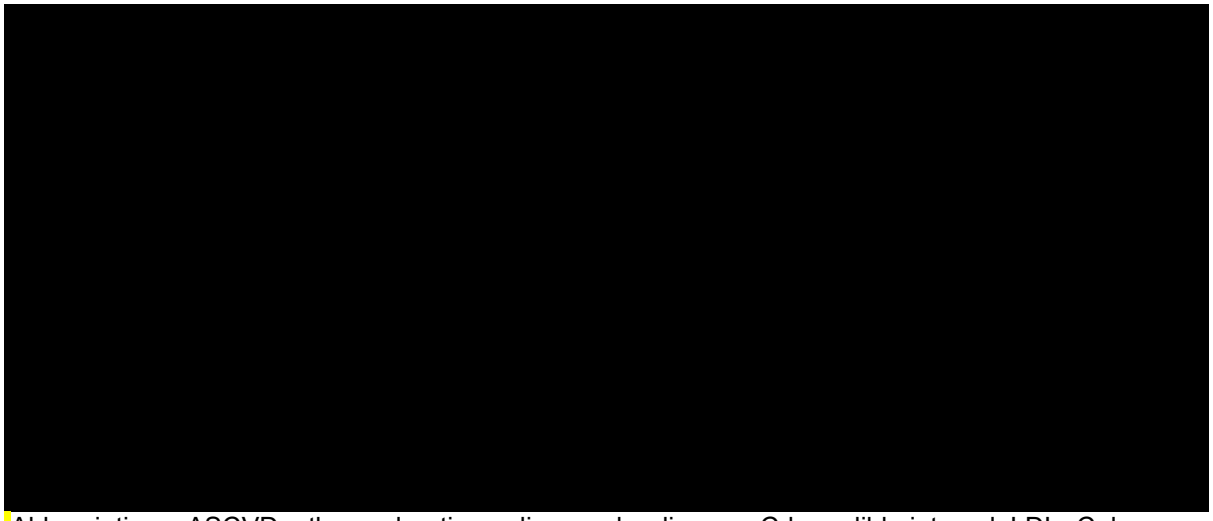
[redacted]

[redacted]

[redacted]

[redacted]

Figure 42: ASCVD Intolerant: Difference in Absolute Change in LDL-C – random effects – Inclisiran versus Other Treatments



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL- C, low-density lipoprotein cholesterol.

Figure 43: ASCVD Intolerant: Difference in Absolute Change in LDL-C – random effects – Treatments versus Placebo

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval; LDL- C, low-density lipoprotein cholesterol; NMA, network meta-analysis.

B.2.9.2.3.2.2 ***Sensitivity Analyses***

[redacted]

Table 45: ASCVD Intolerant: SA Results for Difference in Absolute Change in LDL-C – random effects – Inclisiran versus Other Treatments

Comparator	Difference in Absolute CFB (95% CrI)	Probability Inclisiran is Better
[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: CFB, change from baseline; CrI, credible interval.

B.2.9.2.3.3 Total Discontinuations at ≥24 Weeks

[redacted]

[redacted]

Figure 44: ASCVD Intolerant: Difference in Total Discontinuations – fixed effects – Inclisiran versus Other Treatments


[redacted]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval.

Figure 45: ASCVD Intolerant: Difference in Total Discontinuations – random effects – Treatments versus Placebo


[redacted]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval

B.2.9.2.3.4 Discontinuation Due to AE at ≥24 Weeks

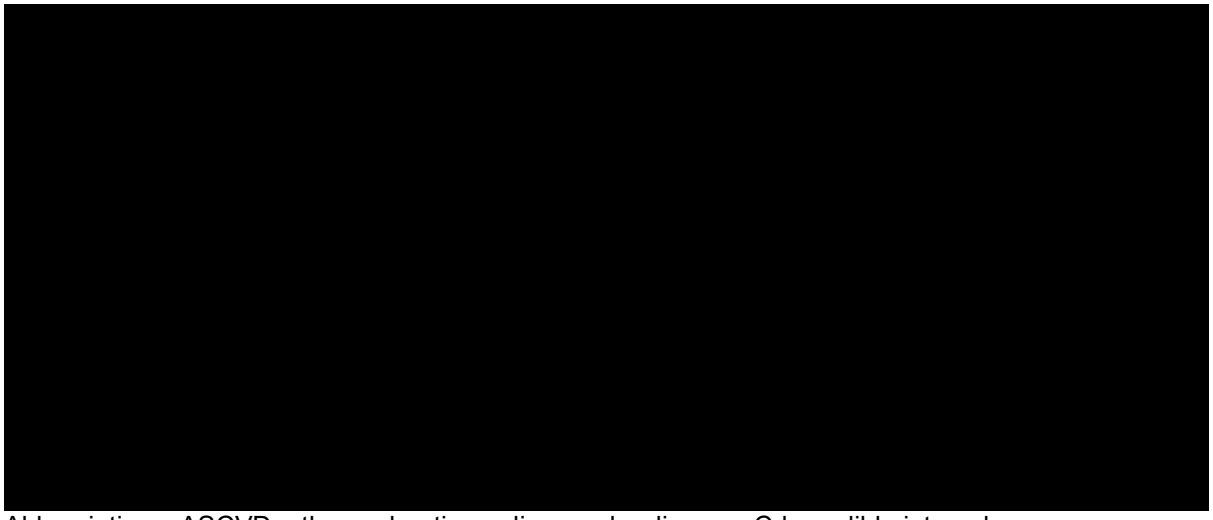
[redacted]

[redacted]

Figure 46: ASCVD Intolerant: Difference in Discontinuations due to AEs – fixed effects – Inclisiran versus Other Treatments

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval

Figure 47: ASCVD Intolerant: Difference in Discontinuations due to AEs – fixed effects – Treatments versus Placebo



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval

B.2.9.2.3.5 Percent Change in HDL-C at 24 Weeks

[redacted]

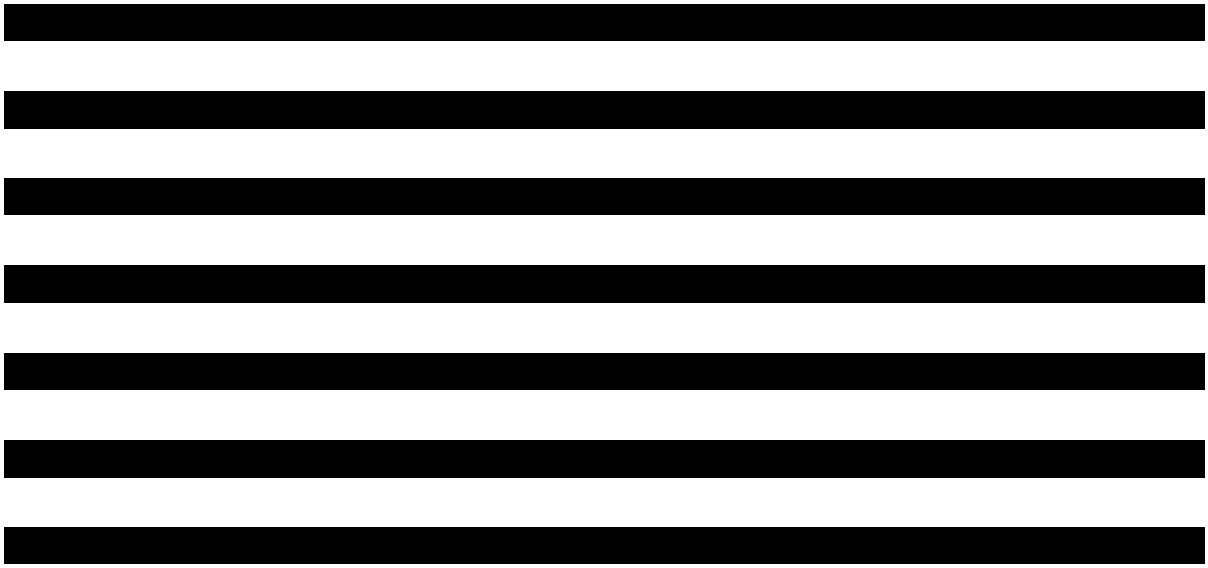


Figure 48: ASCVD Intolerant: Difference in Percent Change in HDL-C – random effects – Inclisiran versus Other Treatments

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval

Figure 49: ASCVD Intolerant: Difference in Percent Change in HDL-C – random effects – Treatments versus Placebo

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CrI, credible interval

B.2.9.2.4 *HeFH population*

B.2.9.2.4.1 Percent Change in LDL-C at 24 Weeks

B.2.9.2.4.1.1 ***Base Case***

[redacted]

Figure 50: HeFH MTD: Difference in percent change in LDL-C – random effects – inclisiran versus other treatments

Abbreviations: CrI, credible interval; HeFH, heterozygous FH; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose.

Figure 51: HeFH MTD: Difference in percent change in LDL-C – random effects – treatments versus placebo

Abbreviations: CrI, credible interval; FH, familial hypercholesterolaemia; HeFH, heterozygous FH; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose; NMA, network meta-analysis.

B.2.9.2.4.1.2 *Sensitivity analyses*

[redacted]

[redacted]

Table 46: HeFH MTD: SA results for difference in percent change in LDL-C – random effects – inclisiran versus other treatments

Comparator	Difference in % CFB (95% CrI)	Probability inclisiran is better
[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]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; CrI, credible interval; SA sensitivity analysis

B.2.9.2.4.2 Absolute Change in LDL-C at 24 Weeks

[redacted]

[redacted]

[redacted]

B.2.9.2.4.2.1 ***Base case***

[redacted]

[redacted]

[redacted]

[redacted]

Figure 52: HeFH MTD: Difference in absolute change in LDL-C – random effects – inclisiran versus other treatments

Abbreviations: CrI, credible interval; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose

Figure 53: HeFH MTD: Difference in absolute change in LDL-C – random effects – treatments versus placebo

[redacted]

Abbreviations: CrI, credible interval; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerated dose; NMA, network meta-analysis

B.2.9.2.4.2.2 *Sensitivity Analyses*

[redacted]

[redacted]

[redacted]

Table 47: HeFH MTD: SA results for difference in absolute change in LDL-C – random effects – inclisiran versus other treatments

Comparator	Absolute Difference in CFB (95% CrI)	Probability Inclisiran is Better
[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]

Abbreviations: CFB, change from baseline; CrI, credible interval.

B.2.9.2.4.3 Total Discontinuations at ≥24 Weeks

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Figure 54: HeFH MTD: Difference in total discontinuations – random effects – inclisiran versus other treatments


[redacted]

Abbreviations: CrI, credible interval; HeFH, heterozygous familial hypercholesterolaemia; MTD, maximally tolerated dose.

Figure 55: HeFH MTD: Difference in total discontinuations – random effects – treatments versus placebo


[redacted]

Abbreviations: CrI, credible interval; HeFH, heterozygous familial hypercholesterolaemia; MTD, maximally tolerated dose.

B.2.9.2.4.4 Discontinuation Due to AEs at ≥24 Weeks

[redacted]

[redacted]

[redacted]

Figure 56: HeFH MTD: Difference in discontinuations due to AEs – fixed effects – inclisiran versus other treatments

Abbreviations: AE, adverse event; Crl, credible interval; HeFH, heterozygous familial hypercholesterolaemia; MTD, maximally tolerated dose.

Figure 57: HeFH MTD: Difference in discontinuations due to AEs – fixed effects – treatments versus placebo

Abbreviations: AE, adverse event; Crl, credible interval; HeFH, heterozygous familial hypercholesterolaemia; MTD, maximally tolerated dose.

B.2.9.2.4.5 Percent Change in HDL-C at 24 Weeks

[redacted]

[redacted]

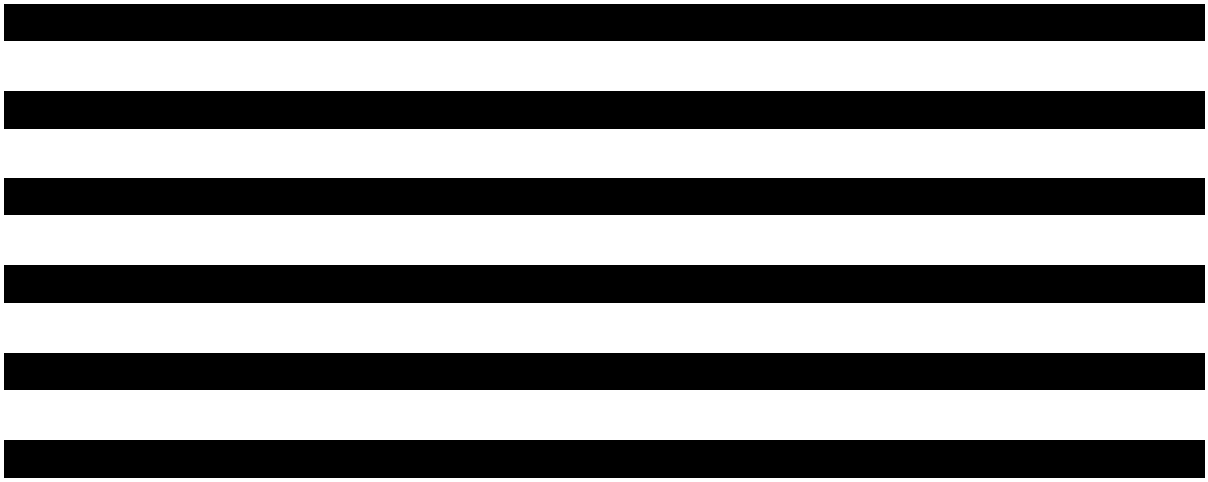


Figure 58: HeFH MTD: Difference in percent change in HDL-C – random effects – inclisiran versus other treatments

Abbreviations: CrI, credible interval; HeFH, heterozygous familial hypercholesterolaemia; MTD, maximally tolerated dose.

Figure 59: HeFH MTD: Difference in percent change in HDL-C – random effects – treatments versus placebo

Abbreviations: CrI, credible interval; HeFH, heterozygous familial hypercholesterolaemia; MTD, maximally tolerated dose.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

[redacted]

B.2.9.4 Conclusions from the NMA

Findings from the NMA show that the addition of inclisiran to current standard of care for patients with ASCVD and HeFH consistently results in statistically significant improvements in LDL-C, HDL-C, and comparable tolerability compared to placebo. While a clinically meaningful improvement in percent change or absolute LDL-C has not been formally established against PCSK9 inhibitors, the NMA findings suggests that inclisiran provides outcomes that are expected to be comparable to alirocumab and evolocumab across various hypercholesteremia patient populations.

B.2.10 Adverse reactions

In all three trials, inclisiran was well-tolerated with a safety profile comparable to placebo (except for injection site reactions). More inclisiran-treated patients reported treatment emergent adverse events (TEAEs) at the injection site than placebo-treated patients. However, all TEAEs at the injection site were localised, predominantly mild or occasionally moderate, transient (i.e. resolving prior to the next dose), and resolved without sequelae.

Summaries of adverse events for ORION-9, 10 and 11 are presented in Sections B.2.10.1–B.2.10.3, and an overall safety summary is presented in Section B.2.10.4.

B.2.10.1 ORION-9

B.2.10.1.1 *Summary of treatment-emergent adverse events*

The incidence of TEAEs, treatment emergent serious adverse events (TESAEs), deaths, and discontinuations due to TEAEs was similar between treatment groups (Table 48).

Table 48: Overall summary of TEAEs (safety population; ORION-9)

Category	Placebo (N=240) n (%)	Inclisiran (N=241) n (%)	Total (N=481) n (%)
≥1 TEAE	172 (71.7)	185 (76.8)	357 (74.2)
≥1 TESAE	33 (13.8)	18 (7.5)	51 (10.6)
≥1 treatment-related TESAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	1 (0.4)	1 (0.4)	2 (0.4)

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

B.2.10.1.2 *Common adverse events*

The incidence and type of common TEAEs was similar between treatment groups. The most common TEAEs (at least 5% in either treatment group) are shown in Table 49.

Table 49: Common (≥5% within either treatment group) TEAEs by preferred term (safety population; ORION-9)

Preferred Term	Placebo (N=240)		Inclisiran (N=241)		Risk ratio[†] (95% CI)
	n (%)	E	n (%)	E	
≥1 TEAE[‡]	172 (71.7)	588	185 (76.8)	663	1.1 (1.0, 1.2)
Nasopharyngitis	20 (8.3)	21	28 (11.6)	36	1.4 (0.8, 2.4)
Influenza	21 (8.8)	24	13 (5.4)	15	0.6 (0.3, 1.2)
Upper respiratory tract infection	16 (6.7)	22	16 (6.6)	19	1.0 (0.5, 1.9)
Back pain	10 (4.2)	11	17 (7.1)	19	1.7 (0.8, 3.6)
Injection site reaction	0 (0.0)	0	22 (9.1)	37	NA

[†]Risk ratio of inclisiran vs placebo
[‡]Includes all patients, not just patients with most common AEs
Abbreviations: AE, adverse event; CI, confidence interval; E, events; NA, not applicable; TEAE, treatment-emergent adverse event.

B.2.10.1.3 *Adverse events related to study drug*

Ten (4.2%) placebo-treated patients experienced TEAEs considered by the investigators as having a reasonable possibility of being related to treatment, compared with 58 (24.1%) inclisiran-treated patients.

This was mostly due to a higher incidence of TEAEs at the injection site in the inclisiran arm (Section B.2.10.1.5). In the placebo arm, none of the TEAEs were reported in more than one patient. In the inclisiran arm, the most common TEAEs considered related to study drug were injection site reaction (22 patients; 9.1%), injection site erythema (9 patients; 3.7%), injection site pain (6 patients; 2.5%), and injection site pruritis (6 patients; 2.5%).

B.2.10.1.4 *Serious adverse events*

There were minimal differences in the nature of TESAEs between the treatment groups, and the prevalence was slightly higher in the placebo arm (33 placebo-treated patients [13.8%] and 18 inclisiran-treated patients [7.5%] (Table 50). These were predominantly CV events, and about one-half of TESAEs in both groups were considered severe.

Table 50: Common (≥1% within either treatment group) treatment-emergent serious adverse events (safety population; ORION-9)

Preferred Term	Placebo (N=240)		Inclisiran (N=241)		Total (N=481)	
	n (%)	E	n (%)	E	n (%)	E
≥1 TESAE	33 (13.8)	48	18 (7.5)	23	51 (10.6)	71
Angina unstable	4 (1.7)	4	1 (0.4)	1	5 (1.0)	5
Myocardial ischaemia	3 (1.3)	3	1 (0.4)	1	4 (0.8)	4
Acute myocardial infarction	1 (0.4)	1	2 (0.8)	2	3 (0.6)	3
Aortic valve stenosis	0 (0.0)	0	2 (0.8)	2	2 (0.4)	2
Back pain	2 (0.8)	2	0 (0.0)	0	2 (0.4)	2

Abbreviations: E, events; TESAE, treatment-emergent serious adverse event.

B.2.10.1.5 *Treatment-emergent adverse events at the injection site*

Four placebo-treated patients (1.7%) reported TEAEs at the injection site (including but not limited to injection site pain, injection site reaction and injection site erythema), compared with 41 inclisiran-treated patients (17.0%). Of these 45

patients, the majority had a mild event (41 patients) and none had a severe event. One inclisiran-treated patient withdrew from study drug due to an injection site reaction (this event was moderate and non-serious). No inclisiran-treated patients experienced a serious TEAE at the injection site.

B.2.10.1.6 *Subgroup analysis*

The adverse event profile of inclisiran was not affected by geographic region, demographic characteristics, baseline disease characteristics, or comorbidities (Appendix E).

B.2.10.2 ORION-10

B.2.10.2.1 *Summary of treatment-emergent adverse events*

The incidence of TEAEs, TESAEs, deaths, and discontinuations due to TEAEs was similar between treatment groups (Table 51).

Table 51: Overall summary of TEAEs (safety population; ORION-10)

Category	Placebo (N=778) n (%)	Inclisiran (N=781) n (%)	Total (N=1,559) n (%)
≥1 TEAE	582 (74.8)	574 (73.5)	1156 (74.2)
≥1 TESAE	205 (26.3)	175 (22.4)	380 (24.4)
≥1 treatment-related TESAE	1 (0.1)	2 (0.3)	3 (0.2)
Discontinued due to TEAE	5 (0.6)	8 (1.0)	13 (0.8)
Deaths	11 (1.4)	12 (1.5)	23 (1.5)

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

B.2.10.2.2 *Adverse events related to study drug*

Eighty-five (10.9%) placebo-treated patients experienced TEAEs considered by the investigators as having a reasonable possibility of being related to treatment, compared with 105 (13.4%) inclisiran-treated patients.

This was mostly due to a higher incidence of TEAEs at the injection site in the inclisiran arm (Section B.2.10.2.4). In the placebo arm, the most common TEAEs considered related to study drug were diabetes mellitus (9 patients; 1.2%), headache (8 patients; 1.0%), and blood creatinine phosphokinase increased (7 patients; 0.9%). In the inclisiran arm, the most common TEAEs considered related to study drug were

injection site pain (23 patients; 2.9%), diabetes mellitus (18 patients; 2.3%), and injection site reaction (13 patients; 1.7%).

B.2.10.2.3 *Serious adverse events*

There were minimal differences in the nature of TESAEs between the treatment groups. The prevalence of TESAEs was slightly higher in the placebo arm (205 patients; 26.3%) than the inclisiran arm (175 patients; 22.4%) (Table 52). TESAEs were predominantly CV events, and more than half of TESAEs were considered severe.

Table 52: Common (≥1% within either treatment group) treatment-emergent serious adverse events (safety population; ORION-10)

Preferred Term	Placebo (N=778)		Inclisiran (N=781)		Total (N=1,559)	
	n (%)	E	n (%)	E	n (%)	E
≥1 TESAE	205 (26.3)	422	175 (22.4)	339	380 (24.4)	761
Coronary artery disease	22 (2.8)	25	15 (1.9)	15	37 (2.4)	40
Cardiac failure congestive	20 (2.6)	30	7 (0.9)	7	27 (1.7)	37
Acute myocardial infarction	12 (1.5)	13	14 (1.8)	15	26 (1.7)	28
Pneumonia	9 (1.2)	9	11 (1.4)	12	20 (1.3)	21
Non-cardiac chest pain	9 (1.2)	9	10 (1.3)	10	19 (1.2)	19
Atrial fibrillation	8 (1.0)	9	10 (1.3)	11	18 (1.2)	20
Chronic obstructive pulmonary disease	8 (1.0)	10	8 (1.0)	10	16 (1.0)	20
Angina unstable	10 (1.3)	12	4 (0.5)	5	14 (0.9)	17

Abbreviations: E, events; TESAE, treatment-emergent serious adverse event.

B.2.10.2.4 *Common adverse events*

The incidence and type of common TEAEs was similar between treatment groups. The most common TEAEs (at least 5% in either treatment group) are shown in Table 55.

Table 53: Common (≥5% within either treatment group) TEAEs by preferred term (safety population; ORION-10)

Preferred Term	Placebo (N=778)		Inclisiran (N=781)		Risk ratio[†] (95% CI)
	n (%)	E	n (%)	E	
≥1 TEAE[‡]	582 (74.8)	2,639	574 (73.5)	2,559	1.0 (0.9, 1.0)

Preferred Term	Placebo (N=778)		Inclisiran (N=781)		Risk ratio† (95% CI)
	n (%)	E	n (%)	E	
Diabetes mellitus	108 (13.9)	113	120 (15.4)	125	1.1 (0.9, 1.4)
Hypertension	42 (5.4)	43	42 (5.4)	43	1.0 (0.7, 1.5)
Back pain	39 (5.0)	41	39 (5.0)	42	1.0 (0.6, 1.5)
Bronchitis	30 (3.9)	38	46 (5.9)	54	1.5 (1.0, 2.4)
Dyspnoea	33 (4.2)	36	39 (5.0)	41	1.2 (0.7, 1.9)

†Risk ratio of inclisiran vs placebo
‡Includes all patients, not just patients with most common AEs
Abbreviations: AE, adverse event; CI, confidence interval; E, events; TEAE, treatment-emergent adverse event.

B.2.10.2.5 *Treatment-emergent adverse events at the injection site*

Fifteen placebo-treated patients (1.9%) reported TEAEs at the injection site (including but not limited to injection site pain, injection site reaction and injection site erythema), compared with 47 inclisiran-treated patients (6.0%). Of the 47 inclisiran-treated patients, the majority had a mild event (40 patients) and none had a severe event. One inclisiran-treated patient withdrew from study drug due to TEAEs at the injection site (the patients had one mild non-serious event). No inclisiran-treated patients experienced a serious TEAE at the injection site.

B.2.10.2.6 *Subgroup analysis*

The adverse event profile of inclisiran was not affected by geographic region, demographic characteristics, baseline disease characteristics, or comorbidities.

B.2.10.3 ORION-11

B.2.10.3.1 *Summary of treatment-emergent adverse events*

The incidence of TEAEs, TESAEs, deaths, and discontinuations due to TEAEs was similar between treatment groups (Table 54).

Table 54: Overall summary of TEAEs (safety population; ORION-11)

Category	Placebo (N=804) n (%)	Inclisiran (N=811) n (%)	Total (N=1,615) n (%)
≥1 TEAE	655 (81.5)	671 (82.7)	1,326 (82.1)
≥1 TESAE	181 (22.5)	181 (22.3)	362 (22.4)
≥1 treatment-related TESAE	4 (0.5)	0 (0.0)	4 (0.2)

Category	Placebo (N=804) n (%)	Inclisiran (N=811) n (%)	Total (N=1,615) n (%)
Discontinued due to TEAE	0 (0.0)	4 (0.5)	4 (0.2)
Deaths	15 (1.9)	14 (1.7)	29 (1.8)

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

B.2.10.3.2 *Common adverse events*

The incidence and type of common TEAEs was similar between treatment groups. The most common TEAEs (at least 5% in either treatment group) are shown in Table 55.

Table 55: Common (≥5% within either treatment group) TEAEs by preferred term (safety population; ORION-11)

Preferred Term	Placebo (N=804)		Inclisiran (N=811)		Risk ratio† (95% CI)
	n (%)	E	n (%)	E	
≥1 TEAE‡	655 (81.5)	2,605	671 (82.7)	2,893	1.0 (1.0, 1.1)
Diabetes mellitus	94 (11.7)	100	88 (10.9)	101	0.9 (0.7, 1.2)
Nasopharyngitis	90 (11.2)	110	91 (11.2)	105	1.0 (0.8, 1.3)
Hypertension	54 (6.7)	59	53 (6.5)	60	1.0 (0.7, 1.4)
Upper respiratory tract infection	49 (6.1)	57	52 (6.4)	59	1.1 (0.7, 1.5)
Arthralgia	32 (4.0)	37	47 (5.8)	56	1.5 (0.9, 2.3)
Osteoarthritis	40 (5.0)	43	32 (3.9)	37	0.8 (0.5, 1.2)

†Risk ratio of inclisiran vs placebo
‡Includes all patients, not just patients with most common AEs
Abbreviations: AE, adverse event; CI, confidence interval; E, events; TEAE, treatment-emergent adverse event.

B.2.10.3.3 *Adverse events related to study drug*

Eighty-two (10.2%) placebo-treated patients experienced TEAEs considered by the investigators as having a reasonable possibility of being related to treatment, compared with 123 (15.2%) inclisiran-treated patients.

This was mostly due to a higher incidence of TEAEs at the injection site in the inclisiran arm (Section B.2.10.3.5). In the placebo arm, the most common TEAEs considered related to study drug were creatine phosphokinase increased (6 patients; 0.7%), myalgia (5 patients; 0.6%), and fatigue (5 patients; 0.6%). In the inclisiran arm, the most common TEAEs considered related to study drug were injection site

reaction (18 patients; 2.2%), injection site erythema (13 patients; 1.6%), diabetes mellitus (8 patients; 1.0%) and injection site pain (8 patients; 1.0%).

B.2.10.3.4 *Serious adverse events*

There were minimal differences in the frequency or nature of TESAEs between the treatment groups (181 placebo-treated patients [22.5%] and 181 inclisiran-treated patients [22.3%] (Table 56). TESAEs were predominantly CV events, and about one-half of TESAEs in both groups were considered severe.

Table 56: Common (≥1% within either treatment group) treatment-emergent serious adverse events (safety population; ORION-11)

Preferred Term	Placebo (N=804)		Inclisiran (N=811)		Total (N=1,615)	
	n (%)	E	n (%)	E	n (%)	E
≥1 TESAE	181(22.5)	293	181 (22.3)	283	362 (22.4)	576
Angina pectoris	13 (1.6)	14	14 (1.7)	14	27 (1.7)	28
Acute myocardial infarction	18 (2.2)	21	5 (0.6)	5	23 (1.4)	26
Angina unstable	11 (1.4)	11	11 (1.4)	12	22 (1.4)	23
Coronary artery disease	11 (1.4)	15	8 (1.0)	8	19 (1.2)	23
Atrial fibrillation	6 (0.7)	7	10 (1.2)	11	16 (1.0)	18
Pneumonia	7 (0.9)	7	9 (1.1)	9	16 (1.0)	16
Peripheral arterial occlusive disease	8 (1.0)	9	7 (0.9)	7	15 (0.9)	16
Non-cardiac chest pain	8 (1.0)	8	4 (0.5)	4	12 (0.7)	12

Abbreviations: E, events; TESAE, treatment-emergent serious adverse event.

B.2.10.3.5 *Treatment-emergent adverse events at the injection site*

Fourteen placebo-treated patients (1.7%) reported TEAEs at the injection site (including but not limited to injection site pain, injection site reaction and injection site erythema), compared with 62 inclisiran-treated patients (7.6%). Of the 62 inclisiran-treated patients, the majority had a mild event (46 patients) and none had a severe event. Two inclisiran-treated patients withdrew from study drug due to TEAEs at the injection site (both patients had one moderate non-serious event). No inclisiran-treated patients experienced a serious TEAE at the injection site.

B.2.10.3.6 *Subgroup analysis*

The adverse event profile of inclisiran was not affected by geographic region, demographic characteristics, baseline disease characteristics, or comorbidities.

B.2.10.4 Overview of the safety of inclisiran

Across the studies, inclisiran was generally well-tolerated, with generally no differences vs placebo in terms of the frequency and nature of adverse events. More inclisiran-treated patients reported TEAEs at the injection site than placebo-treated patients (8.2% vs 1.8% experienced TEAEs at the injection site, respectively, across the studies; 0.2% vs 0.0% discontinued due to these TEAEs, respectively [Appendix C]). However, all of these were localised, predominantly mild or occasionally moderate, transient (i.e. resolving prior to the next dose), and resolved without sequelae.

There were no differences in hepatic, renal, and diabetic safety parameters compared with placebo, and the safety profile of inclisiran was consistent across all subgroups.

B.2.11 Ongoing studies

ORION-4 and ORION-8 are not expected to provide additional evidence in the next 12 months but have been included here as they will provide key outcomes data in this population. ORION-4 and ORION-8 are expected to read out in 2024 and 2023, respectively.

A Novartis-supported trial designed to assess the implementation of inclisiran in a primary care setting will begin recruiting patients in February 2021. The SPIRIT study (Study in Primary care evaluating Inclisiran deliveRy Implementation + enhanced SupporT) is an innovative study using an established Implementation Science approach integrated with a Phase 3b efficacy and safety design.

B.2.11.1 ORION-4

ORION-4 (NCT03705234) is a double-blind, randomised placebo-controlled assessment of the effects of inclisiran on clinical outcomes in approximately 15,000 patients with pre-existing ASCVD. Follow-up of all randomised participants is

scheduled to continue for a median of approximately 5 years and until at least 1,700 participants have experienced a primary outcome following randomisation.

The primary efficacy outcome measure is the clinically relevant composite of coronary heart disease (CHD) death, MI, fatal or non-fatal IS, or urgent coronary revascularisation.

Key secondary outcomes include time to first occurrence of the composite outcome of CHD death or MI, and CV death.

B.2.11.2 ORION-8

ORION-8 (NCT03814187) is an open-label extension study for patients who completed ORION-9, 10 and 11. The purpose of this extension study is to evaluate the efficacy, safety, and tolerability of long-term dosing of inclisiran. Each patient is expected to be enrolled for a maximum of 3 years (or until discontinuation, an administrative decision to end the study, or regulatory approval for inclisiran in the respective country).

The primary objectives of the study are to evaluate the effect of inclisiran treatment on the proportion of patients achieving pre-specified LDL-C targets at the end of the study, and the safety and tolerability of long-term use of inclisiran.

The secondary objectives are to evaluate the effect of inclisiran on levels of LDL-C, other lipids and lipoproteins.

B.2.11.3 SPIRIT

The SPIRIT study will focus on testing clinical intervention with inclisiran in a real-world situation (in this case primary care) while observing and gathering information on its ‘implementability’.

The study will recruit 900 patients divided between 3 treatment groups (standard of care + behavioural support, inclisiran + behavioural support, or inclisiran only) and follow patients for a 9-month period. With a combination of interventional, observational and qualitative assessments, and utilising the electronic medical record, the objectives of the study are:

- to demonstrate the superiority of inclisiran with or without behavioural support compared to standard of care with behavioural support on LDL-C
- to evaluate the implementation of inclisiran with or without behavioural support compared to standard of care with behavioural support on measures of patient and healthcare professional satisfaction, patient activation and patient adherence
- to use the Consolidated Framework for Implementation Research (CFIR) which will explore inclisiran delivery
- to assess the serious adverse event profile in this setting.

The full clinical study report is expected in August 2022.

B.2.12 Innovation

B.2.12.1 Inclisiran has a novel mode of action and requires less frequent dosing compared with PCSK9 inhibitors

Inclisiran is the first and only cholesterol-lowering siRNA, representing a step-change in the management of LDL-C levels (and consequently CV event risk) in patients with ASCVD, HeFH and PPER. The introduction of this treatment into the lipid management treatment pathway could potentially transform how LDL-C lowering is approached by regional and local NHS.

Statins do not provide adequate reductions in LDL-C for some patients at high risk of CV events due to insufficient efficacy, low tolerability, and poor adherence (Section B.1.3.6.2). PCSK9 inhibitors and ezetimibe are the current standard-of-care (SoC) for patients who require further LDL-C lowering despite maximally tolerated statin therapy (Section B.1.3.5.4). However, in the case of PCSK9 inhibitors these are associated with fortnightly or monthly subcutaneous dosing, which results in patient burden and may impact adherence given the more frequent dosing compared with inclisiran. Non-adherence to lipid-lowering therapy contributes substantially to poor outcomes in CVD (62, 110). Furthermore, PCSK9 inhibitors are only available to patients with higher LDL-C levels (Figure 3).

Results from ORION-9, 10 and 11 demonstrate that inclisiran administration every 6 months (after initial and 3-month doses) is well-tolerated (with a safety profile comparable to placebo, except for injection site reactions), resulting in sustained and effective LDL-C reductions comparable to those observed with fortnightly or monthly dosing of PCSK9 inhibitors. The NMA findings suggest that inclisiran provides outcomes expected to be comparable to alirocumab and evolocumab across various hypercholesteremia patient populations.

The combination of inclisiran's sustained efficacy and twice-a-year maintenance dosing means that the treatment provides the potential to help patients reach their LDL-C goals with minimal administration requirements for the healthcare system and minimal additional burden on the patient.

B.2.12.2 Implementation of inclisiran in primary care

Cardiovascular disease is one of the health conditions most strongly associated with health inequalities, driving the life expectancy gap as the greatest cause of premature mortality in areas of deprivation, with 40% of all amenable deaths in CVD in the three most deprived deciles (64). Simon Stevens has requested that Chief Executives of all NHS Trusts and Foundation Trusts work collaboratively with local communities and partners to take urgent action to increase the scale and pace of progress of reducing health inequalities, and to accelerate preventative programmes which proactively engage those at greatest risk of poor health outcomes, including better targeting of long-term condition prevention and management programmes (111).

Unwarranted variation in the uptake of innovative products that are delivered exclusively in secondary care is well established. In the cardiovascular field, Novartis has recent data demonstrating that uptake of sacubitril valsartan ranges from as [redacted] of the NICE-eligible patient population across localities within England.

Under the framework of the inclisiran population health collaboration with NHS England, inclisiran will potentially be delivered [redacted] within primary care using proactive care delivery models, making full use of the recently established Primary Care Networks (PCNs) in order to reduce the

burden on outpatient and secondary care departments. This is expected to improve equality in care provision, compared current situation in which there is geographical variation in the accessibility and maturity of lipid clinics.

High-quality community services underpinned by strong integration between secondary care and community care are one of several factors that lead to better management of patients with cardiovascular diseases. The use of PCNs to optimise treatment of high-risk conditions using new models and pathways to systematically case-find under-treated patients is aligned with the NHS Long Term Plan to prevent up to 150,000 heart attacks, strokes and dementia cases over the next 10 years.

Significant activity is underway with the Accelerated Access Collaborative to support delivery of the population health model and appropriate uptake of inclisiran, which is expected to represent a step-change in the management of patients with [redacted]. The improved equality of access to highly-effective lipid-lowering therapy throughout England that the inclisiran population health model offers, represents a benefit that cannot be captured in the QALY.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The eligibility criteria for ORION-9, 10 and 11 ensured that the trial populations were representative of the patient populations likely to be treated with inclisiran in clinical practice. Study completion rates were high, with 97%, 90% and 95% of patients completing the ORION-9, 10 and 11 studies, respectively.

Across the three trials, treatment with inclisiran resulted in a 47.9%–52.3% placebo-adjusted reduction in LDL-C at Day 510, and a 44.3%–53.8% time-adjusted reduction in LDL-C after Day 90 and up to Day 540. LDL-C targets were met by 77% (ORION-9), 94% (ORION-10) and 92% (ORION-11) of patients. These results would be expected to translate into a clinically meaningful reduction in risk of CV events. Further studies are ongoing to assess the impact of inclisiran treatment on CV event reduction (Section 0).

The response to inclisiran was consistent across all patients regardless of baseline demographic and baseline disease characteristics, comorbidities, and geographic

regions. This consistent and robust LDL-C lowering effect is likely related to inclisiran's unique mode of action.

Treatment with inclisiran over 18 months was well tolerated and, except for injection site reactions, demonstrated a safety profile comparable to placebo. The only TEAEs considered related to inclisiran treatment were TEAEs at the injection site, which occurred more frequently with inclisiran than placebo. The incidence of TEAEs at the injection site was low, the majority resolved without sequelae, and all were mild or moderate in severity. No inclisiran-treated patient had a TESAE at the injection site.

These results suggest that sustained reductions in LDL-C levels are achievable with the twice-yearly maintenance dosing schedule of inclisiran. This dosing approach has the potential to enable optimal adherence which may, in turn, support the maintenance of LDL-C reductions over the long-term.

B.3 Cost effectiveness

The cost-effectiveness analysis showed that inclisiran is a cost-effective treatment option for ASCVD with a baseline LDL-C of ≥2.6 mmol/L, PPER with a baseline LDL-C of ≥2.6 mmol/L, and primary prevention HeFH with a baseline LDL-C of >4 mmol/L.

The economic analysis considers the following populations:

- 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 (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 economic model is based on the model used in TA393 and comprised of 3 initial states, whose characteristics vary according to the population being modelled, post event states for revascularisation, UA, MI, IS and states for CV and non-CV death
- Baseline risks were taken from an analysis of the CPRD database, which provides 1-year event probabilities for revascularisation, UA, MI, IS and CV death for each population. These rates are adjusted to reflect the baseline age and LDL-C of the population of interest in the ORION clinical studies. The treatment effect is modelled as percent change from baseline LDL-C, with the values for inclisiran and each comparator being taken from the NMA. Changes in LDL-C are then converted into changes in the rates of CV events using data from the CTT meta-analysis
- HRQoL data is taken from the Ara and Brazier study used in TA393 and the cost of CV events is informed by CG181 and NHS reference costs. The cost of SoC assumes the same split of patients across high, medium and low

intensity statins and ezetimibe as was observed in the ORION clinical studies

- [redacted]
- [redacted]
- These results are confirmed by the sensitivity analysis, with the PSA demonstrating a high level of certainty in the ICERs and little variation in the scenario analyses. [redacted]

B.3.1 Published cost-effectiveness studies

- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology appraisal).
- See section 3.1 of the user guide for full details of the information required in appendix G.

A systematic literature review was conducted to identify relevant cost-effectiveness studies. Appendix G contains the full details of the process and methods used in the cost-effectiveness SLR.

In total, 63 studies and 15 HTAs were identified evaluating the cost-effectiveness of interventions in patients with ASCVD, HeFH, or PPER. Of the included 63 studies, 19 studies were evaluating PCSK9 inhibitors and the remaining 44 studies assessed interventions other than PCSK9 inhibitors such as statins or ezetimibe.

A summary of the six included UK studies is provided in Table 57. Details of other included studies are provided in Appendix G.

Table 57: Summary list of published UK cost-effectiveness studies

<table>
<tr><th>Study</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs, costs (intervention, comparator) and ICER per QALY gained</th><th>Applicability to decision making in England</th></tr>
<tr>
<td>Ara et al. 2012 (112)</td>
<td>UK, Payer perspective (healthcare perspective)</td>
<td>CUA
Comparing high-dose statins (simvastatin 40 mg/day) and moderate-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day)
A cohort-based Markov model was developed with life time horizon and WinBUGS was used for modelling
Utility values were measured using EQ-5D
Costs were expressed in £ (cost year, 2007)
Both costs and QALY were discounted at 3.5% per year</td>
<td>Patients with ACS</td>
<td>
<table>
<tr><th>Base-case/ Scenarios</th><th>Intervention</th><th>Comparator</th><th>Intervention costs (£)</th><th>QALY/ LY</th><th>Comparator costs (£)</th><th>QALY/ LY</th><th>ICER (£/QALY)</th></tr>
<tr><td rowspan="2">Base-case, Scenario A</td><td>A80</td><td>S40</td><td>18,572,000</td><td>QALY: 7,778 LY: 12,033</td><td>14,522,000</td><td>QALY: 7,546 LY: 11,686</td><td>17,469</td></tr>
<tr><td>R40</td><td>S40</td><td>18,464,000</td><td>QALY: 7,862 LY: 12,158</td><td>14,522,000</td><td>QALY: 7,546 LY: 11,686</td><td>12,484</td></tr>
<tr><td rowspan="2">Base-case, Scenario B</td><td>A80</td><td>S40</td><td>17,971,000</td><td>QALY: 7,507 LY: 11,635</td><td>15,232,000</td><td>QALY: 7,383 LY: 11,448</td><td>21,938</td></tr>
<tr><td>R40</td><td>S40</td><td>17,851,000</td><td>QALY: 7,540 LY: 11,685</td><td>15,232,000</td><td>QALY: 7,383 LY: 11,448</td><td>16,592</td></tr>
<tr><td rowspan="2">Base-case, Scenario C</td><td>A80</td><td>S40</td><td>18,042,000</td><td>QALY: 7,748 LY: 11,991</td><td>14,547,000</td><td>QALY: 7,545 LY: 11,688</td><td>17,217</td></tr>
<tr><td>R40</td><td>S40</td><td>17,940,000</td><td>QALY: 7,821 LY: 12,101</td><td>14,547,000</td><td>QALY: 7,545 LY: 11,688</td><td>12,277</td></tr>
</table>
Sensitivity analysis: The incremental cost-effectiveness ratios (ICERs) decrease with starting age of treatment as would be expected, reflecting the higher risk of the older population and thus the potential to avoid events. When decreasing the utilities for all health states, the ICERs increase by approximately 14% reflecting the decrease in benefits from events avoided. Conversely, increasing the utilities decreases the ICERs by approximately 25%. It was assumed that utility values for the post-event health states increased by 10% in the base-case and results were robust to changes in this assumption. While the results are also robust to changes in health state costs, if it is assumed there are no additional monitoring costs associated with the more potent doses, the ICERs are reduced by approximately 20%.
</td>
<td>Applicable for the UK since the evaluation was set in the UK payer perspective</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs, costs (intervention, comparator) and ICER per QALY gained</th><th>Applicability to decision making in England</th></tr>
<tr>
<td>Becerra et al. 2015 (113)</td>
<td>UK, Payer perspective (NHS and the Personal Social Services of the UK)</td>
<td>CUA
comparing: Polypill (100 mg aspirin, 20 mg atorvastatin and 2.5, 5, or 10 mg ramipril) to Monocomponent
A cohort-based Markov model was developed with 3 month cycle length and a 10-year time horizon
Health states were secondary prevention states: recent post-MI and non-recent MI), ACS (MI or angina (acute]), unplanned revascularisation, CHF requiring hospitalisation (acute), stroke (acute), post ACS (chronic), post CHF (chronic), post stroke (chronic) and death</td>
<td>ASCVD</td>
<td>
<table>
<tr><th>Base-case/ Scenarios</th><th>Interve ntion</th><th>Comparator</th><th>Intervention costs (£)</th><th>QALY/ LY</th><th>Comparator costs (£)</th><th>QALY/ LY</th><th>ICER (£/QALY)</th></tr>
<tr><td>Base-case</td><td>Polypill</td><td>Monocomponents</td><td>3,994,814</td><td>QALY: 5278.46; LY: 6338.57</td><td>3,752,473</td><td>QALY: 5,248.92 LY: 6,307.69</td><td>8,205</td></tr>
<tr><td>PSA</td><td>Polypill</td><td>Monocomponents</td><td>-</td><td>-</td><td>-</td><td>-</td><td>WTP of £20,000: 81.5%</td></tr>
<tr><td></td><td>Polypill</td><td>Monocomponents</td><td>-</td><td>-</td><td>-</td><td>-</td><td>WTP of £30,000: 84.8%</td></tr>
</table>
Sensitivity analysis: Incremental costs to be most sensitive to polypill adherence, discount rate and revascularisation costs, while incremental QALYs and ICERs were most sensitive to utility values of patients on secondary prevention and patients having had a second MI.
</td>
<td>Applicable for the UK since the evaluation was set in the perspective of NHS and the Personal Social Services of the UK</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs, costs (intervention, comparator) and ICER per QALY gained</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td>Costs were expressed in £ (cost year, 2014)
Both costs and QALY were discounted at 3.5% per year</td><td></td><td></td><td></td></tr>
<tr><td>Reckless et al. 2010 (114)</td><td>UK, Payer perspective (UK Department of Health perspective)</td><td>CUA
Comparing ezetimibe and simvastatin (10/40 mg) with doubling the submaximal statin therapy [stratum 1: low-potency (fluvastatin 40 mg; pravastatin 10 and 20 mg; Simva 10 mg); stratum 2: medium-potency (atorvastatin 10 mg; Simva 20 mg); and stratum 3: higher-potency (atorvastatin 20 and 40 mg; rosuvastatin 10 and 20 mg; and Simva 40 mg)]
A patient-level Markov model</td><td>Patients with ACS-related events</td><td><table><tr><th>Base-case/Scenarios</th><th>Intervention</th><th>Comparator</th><th>ICER (£/QALY)</th></tr><tr><td>Base-case: Pooled</td><td>EZE/ SIM</td><td>Doubling the statin dose</td><td>11,571</td></tr><tr><td>Base-case: Low-potency (stratum 1)</td><td>EZE/ SIM</td><td>Doubling the statin dose</td><td>13,552</td></tr><tr><td>Base-case: Medium-potency (stratum 2)</td><td>EZE/ SIM</td><td>Doubling the statin dose</td><td>11,930</td></tr><tr><td>Base-case: High-potency (stratum 3)</td><td>EZE/ SIM</td><td>Doubling the statin dose</td><td>10,148</td></tr><tr><td>Base-case: Assuming cost of generic simvastatin for atorvastatin</td><td>EZE/ SIM</td><td>Doubling the statin dose</td><td>17,616</td></tr></table></td><td>Applicable for the UK since the evaluation was set in the UK Department of Health perspective</td></tr>
</table>

<table>
<tr><th>Study</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs, costs (intervention, comparator) and ICER per QALY gained</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td>was developed, with an 1-year cycle length and a lifetime time horizon
• Health states were: No event, MI, angina, CHD death, non-CHD death
• Costs were expressed in £ (cost year, 2004)
• Both costs and QALY were discounted at 3.5% per year</td><td></td><td></td><td></td></tr>
<tr><td>Nherera et al. 2010 (115)</td><td>UK, Payer perspective (UK NHS costing)</td><td>CUA
• comparing high-intensity statin (Atorvastatin 80 mg) with low-intensity statin (simvastatin 40 mg)
• A cohort-based Markov model was developed with lifetime time horizon</td><td>Patients with FH</td><td>
<table>
<tr><th>Base-case/ Scenarios</th><th>Intervention</th><th>Comparator</th><th>Intervention costs (£)</th><th>QALY</th><th>Comparator costs (£)</th><th>QALY</th><th>ICER (£/QALY)</th></tr>
<tr><td>Base-case: FH patients aged 40–59 at diagnosis</td><td>High intensity statin</td><td>Low intensity statin</td><td>14,095</td><td>12.44</td><td>9,448</td><td>12.02</td><td>11,103</td></tr>
<tr><td>PSA</td><td>High intensity statin</td><td>Low intensity statin</td><td>-</td><td>-</td><td>-</td><td>-</td><td>WTP of £20,000: 91%</td></tr>
</table>
</td><td>Applicable for UK since the evaluation was set in the UK NHS costing perspective</td></tr>
</table>

<table>
<tr><th>Study</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs, costs (intervention, comparator) and ICER per QALY gained</th><th>Applicability to decision making in England</th></tr>
<tr><td></td><td></td><td>Health states were ‘well state’, MI, stroke, PAD, HF, revascularisation, unstable angina and death
Costs were expressed in £ (cost year, 2008-2009)
Both costs and QALY were discounted at 3.5% per year</td><td></td><td></td><td></td></tr>
<tr><td>Ferket et al. 2017 (116)</td><td>UK, Payer perspective (UK health system perspective)</td><td>CUA
CUA comparing polypill (simvastatin, amlodipine, losartan, hydrochlorothiazide), old treatment guidelines, current treatment guidelines and alternative guidelines
A patient-level microsimulation model (UK PReventiOn of</td><td>CVD risk patients (population was selected from UK Biobank participants attending baseline visits between 2006 and 2010)</td><td>
<table>
<tr><th>Base-case/ Scenarios</th><th>Intervention</th><th>Comparator</th><th>Intervention costs (£)</th><th>QALY</th><th>Comparator costs (£)</th><th>QALY</th><th>ICER (£/QALY)</th></tr>
<tr><td rowspan="3">Base-case: CV risk assessment scenarios</td><td>OG</td><td>CP</td><td>1,999</td><td>13.38</td><td>1,854</td><td>13.367</td><td>11,797</td></tr>
<tr><td>CG</td><td>CP</td><td>2,064</td><td>13.381</td><td>1,854</td><td>13.367</td><td>(40,089; ED)</td></tr>
<tr><td>AG</td><td>CP</td><td>2,107</td><td>13.38</td><td>1,854</td><td>13.367</td><td>AD</td></tr>
<tr><td>Polypill scenario</td><td>Polypill age 60+</td><td>CP</td><td>3,082</td><td>13.407</td><td>1,854</td><td>13.367</td><td>39,945</td></tr>
<tr><td>Polypill scenario</td><td>Polypill age 55+</td><td>CP</td><td>3,331</td><td>13.406</td><td>1,854</td><td>13.367</td><td>AD</td></tr>
<tr><td>Polypill scenario</td><td>Polypill age 50+</td><td>CP</td><td>3,523</td><td>13.404</td><td>1,854</td><td>13.367</td><td>AD</td></tr>
<tr><td>Polypill scenario</td><td>Polypill age 45+</td><td>CP</td><td>3,645</td><td>13.401</td><td>1,854</td><td>13.367</td><td>AD</td></tr>
<tr><td>Polypill scenario</td><td>Polypill age 40+</td><td>CP</td><td>3,686</td><td>13.4</td><td>1,854</td><td>13.367</td><td>AD</td></tr>
</table>
Sensitivity analysis: In Scenario analyses (No additional prescription of statins in elderly regardless of 10-year CVD risk, periodic cardiovascular risk assessment until age 75-85 years in old guidelines, different uptake of preventive programmes for age ≥55 vs age <55: odds ratio equals 2, adherence to periodic risk assessment in diabetics equal to non-diabetics, full adherence to prevention programmes and preventive medication use, prescription of polypill if eligible age and SBP ≥120-140 mm Hg), alternative guidelines and polypill dominated over current practice. In PSA:</td><td>Applicable for the UK since the evaluation was set in the payer perspective of UK health system</td></tr>
</table>

Study	Country and perspective	Summary of model	Patient population	QALYs, costs (intervention, comparator) and ICER per QALY gained	Applicability to decision making in England
		Myocardial Infarction and Stroke Evaluation (UK-PROMISE) model) was developed with lifetime horizon and 1-year cycle length. treeAge Pro software was used as modelling software • Utility values were measured using EQ-5D • Costs were expressed in £ (cost year, 2012/2013) • Both costs and QALY were discounted at 3.5% per year		cardiovascular risk assessment scenarios, % cost-effective at £30 k/QALY ranged from 0.2 to 24.6 and in PSA: polypill scenario, % cost-effective at £30 k/QALY ranged from 0 to 29	

<table>
<tr><th>Study</th><th>Country and perspective</th><th>Summary of model</th><th>Patient population</th><th>QALYs, costs (intervention, comparator) and ICER per QALY gained</th><th>Applicability to decision making in England</th></tr>
<tr>
<td>Jowett et al. 2017 (117)</td>
<td>UK, Payer perspective (UK NHS and personal social services perspective)</td>
<td>CUA
comparing polypill (simvastatin, hydrochlorothiazide, lisinopril, amlodipine), current treatment (statin) and guideline strategies
A cohort-based Markov model was developed with 10-year time horizon and 1-year cycle length. treeAge pro was used as modelling software
Utility values were measured using EQ-5D
Costs were expressed in £ (cost year, 2011/2012)
Both costs and QALY were discounted at 3.5% per year</td>
<td>Patients aged ≥40 years prescribed a statin and/or blood pressure lowering therapy with no history of CVD</td>
<td>
<table>
<tr><th>Base-case/ Scenarios</th><th>Intervention</th><th>Comparator</th><th>Intervention costs (£)</th><th>QALY</th><th>Comparator costs (£)</th><th>QALY</th><th>ICER (£/QALY)</th></tr>
<tr><td rowspan="3">Base-case: Men; Aged 40-49</td><td>OGC</td><td>CP</td><td>1,634</td><td>7.216</td><td>1,625</td><td>7.202</td><td>604</td></tr>
<tr><td>Polypill</td><td>OGC</td><td>1,878</td><td>7.229</td><td>1,634</td><td>7.216</td><td>18,057</td></tr>
<tr><td>Polypill</td><td>CP</td><td>1,878</td><td>7.229</td><td>1,625</td><td>7.202</td><td>9,166</td></tr>
<tr><td rowspan="3">Base-case: Men; Aged 50-59</td><td>OGC</td><td>CP</td><td>2,013</td><td>6.765</td><td>2,008</td><td>6.74</td><td>182</td></tr>
<tr><td>Polypill</td><td>OGC</td><td>2,136</td><td>6.784</td><td>2,013</td><td>6.765</td><td>6,466</td></tr>
<tr><td>Polypill</td><td>CP</td><td>2,136</td><td>6.784</td><td>2,008</td><td>6.74</td><td>2,897</td></tr>
<tr><td rowspan="3">Base-case: Men; Aged 60-69</td><td>CP</td><td>OGC</td><td>2,343</td><td>6.477</td><td>2,315</td><td>6.524</td><td>Dominated</td></tr>
<tr><td>Polypill</td><td>OGC</td><td>2,386</td><td>6.539</td><td>2,315</td><td>6.524</td><td>4,791</td></tr>
<tr><td>Polypill</td><td>CP</td><td>2,386</td><td>6.539</td><td>2,343</td><td>6.477</td><td>698</td></tr>
<tr><td rowspan="3">Base-case: Men; Aged 70-74</td><td>CP</td><td>OGC</td><td>2,457</td><td>5.853</td><td>2,429</td><td>5.916</td><td>Dominated</td></tr>
<tr><td>Polypill</td><td>OGC</td><td>2,459</td><td>5.922</td><td>2,429</td><td>5.916</td><td>5,068</td></tr>
<tr><td>Polypill</td><td>CP</td><td>2,459</td><td>5.922</td><td>2,395</td><td>4.692</td><td>33</td></tr>
<tr><td rowspan="3">Base-case: Men; Aged 75+</td><td>Polypill</td><td>OGC</td><td>2,327</td><td>4.781</td><td>2,320</td><td>4.782</td><td>Dominated</td></tr>
<tr><td>CP</td><td>Polypill</td><td>2,395</td><td>4.692</td><td>2,327</td><td>4.781</td><td>Dominated</td></tr>
<tr><td>Polypill</td><td>CP</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Dominant</td></tr>
</table>
Sensitivity analysis: Deterministic sensitivity analyses for men aged 60-69 demonstrated that the superior cost effectiveness of a polypill over optimal guideline care over was robust to some underlying assumptions made in the model, with some key exceptions. Optimal guidelines became the most favourable strategy if take up of a polypill was low, if polypill was associated with a small reduction in quality of life, if polypill was less effective than assumed, and if the population was restricted to those with uncontrolled risk factors only . The results were particularly sensitive to the cost of the polypill, with dominance achieved by halving the price or further reducing to the cost of the individual components
</td>
<td>Applicable for the UK since the evaluation was set in the payer perspective of UK NHS and personal social services</td>
</tr>
</table>

Abbreviations: A80, Atorvastatin 80 mg; ACS, acute coronary syndrome; AD, absolutely dominated; AG, alternative guidelines; ASCVD, atherosclerotic cardiovascular disease; BNF, British National Formulary; CHD, coronary heart disease; CP, current practice; CUA, cost utility analysis; CVD, cardiovascular disease; EQ-5D, EuroQoL-5 dimensions; FH, familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LY, life year; MI, myocardial infarction; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OGC, optimal guideline care; ; PSA: Probabilistic sensitivity analysis; QALY, quality-adjusted life years; R40, rosuvastatin; SIM, simvastatin; S40, simvastatin; UK, United Kingdom; WTP: Willingness to pay.

B.3.2 Economic analysis

No economic evaluations of inclisiran in hypercholesterolaemia or mixed dyslipidaemia were identified in the cost-effectiveness SLR. A single economic evaluation was identified after the cost-effectiveness SLR was conducted (118). However, this paper takes the perspective of the Australian healthcare payer and does not cover all relevant populations. It was therefore necessary to develop a de novo cost-effectiveness model. Economic evaluations used in previous NICE appraisals in primary hypercholesterolaemia or mixed dyslipidaemia were used to inform the model's structure, assumptions and data sources (11, 12).

B.3.2.1 Patient population

The economic analysis considers the following populations:

- 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 (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.

As described in Table 1, these populations are narrower than the populations for which marketing authorisation is granted to reflect the available clinical evidence, and as they specify a 2.6 mmol/L LDL-C threshold. These are the populations in which inclisiran is expected to provide the greatest clinical benefit, based on absolute risk reduction observed in trials of PCSK9 inhibitors (18).This threshold has historically been considered a threshold for up-titration and add-on therapy for PCSK9 inhibitors (19) and clinical experts in the UK have recommended a 2.6 mmol/L threshold (Section). Furthermore, this threshold aligns approximately with the mean baseline LDL-C levels in ORION-10 and ORION-11 (Section B.2.3.6).

These populations are considered separately throughout the economic evaluation as patient characteristics (Section B.2.3.6) and treatment recommendations (Table 59) differ between patients with familial and non-familial hypercholesterolaemia and by presence of ASCVD (9, 11, 12, 52, 53).

These populations contain patients who are and are not contraindicated or intolerant to statins. Please note, this does not assume that the patient characteristics between the statin tolerant and intolerant populations are the same. Rather, the patient characteristics considered, risks, and background therapies received in the populations reflect the combined characteristics of both those who are tolerant and contraindicated or intolerant to statins, as represented in the ORION clinical trial programme, across which 651 (17.8%) patients with partial and complete statin intolerance (<8% with complete statin intolerance) were included (21).

B.3.2.1.1 *Subgroups*

The populations were further stratified by presence of HeFH, severity of hypercholesterolemia and statin intolerance or contraindication (Table 58), in line with the NICE scope (Section B.1.1).

Table 58: Subgroups included in the economic model

	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 (11, 12), summarised in Table 59.

Table 59: LDL-C concentrations above which alirocumab and evolocumab are recommended

Population	Without CVD	With CVD	
		High risk of CVD†	Very high risk of CVD‡
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/L	Recommended only if LDL-C concentration is persistently above 3.5 mmol/L
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/L	Recommended only if LDL-C concentration is persistently above 3.5 mmol/L	

Source: NICE TA393 and TA394 (11, 12).
†High risk of CVD is as a history of any of the following: ACS (such as MI or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; CHD; ischaemic stroke; PAD.
‡Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).
Abbreviations: CVD, cardiovascular disease, LDL-C, low-density lipoprotein cholesterol.

B.3.2.2 Model structure

The model structure is based principally on that presented in the manufacturer submission for NICE TA393 (Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia) (11). A 1-year cycle length is used, with half-cycle correction implemented based on the life-table method. The model allows annual transitions from one health state to another based on the predicted risks of CV events (fatal and non-fatal) and the risk of death from non-CV causes.

Event definitions are presented in Table 60.

Table 60: Event definitions

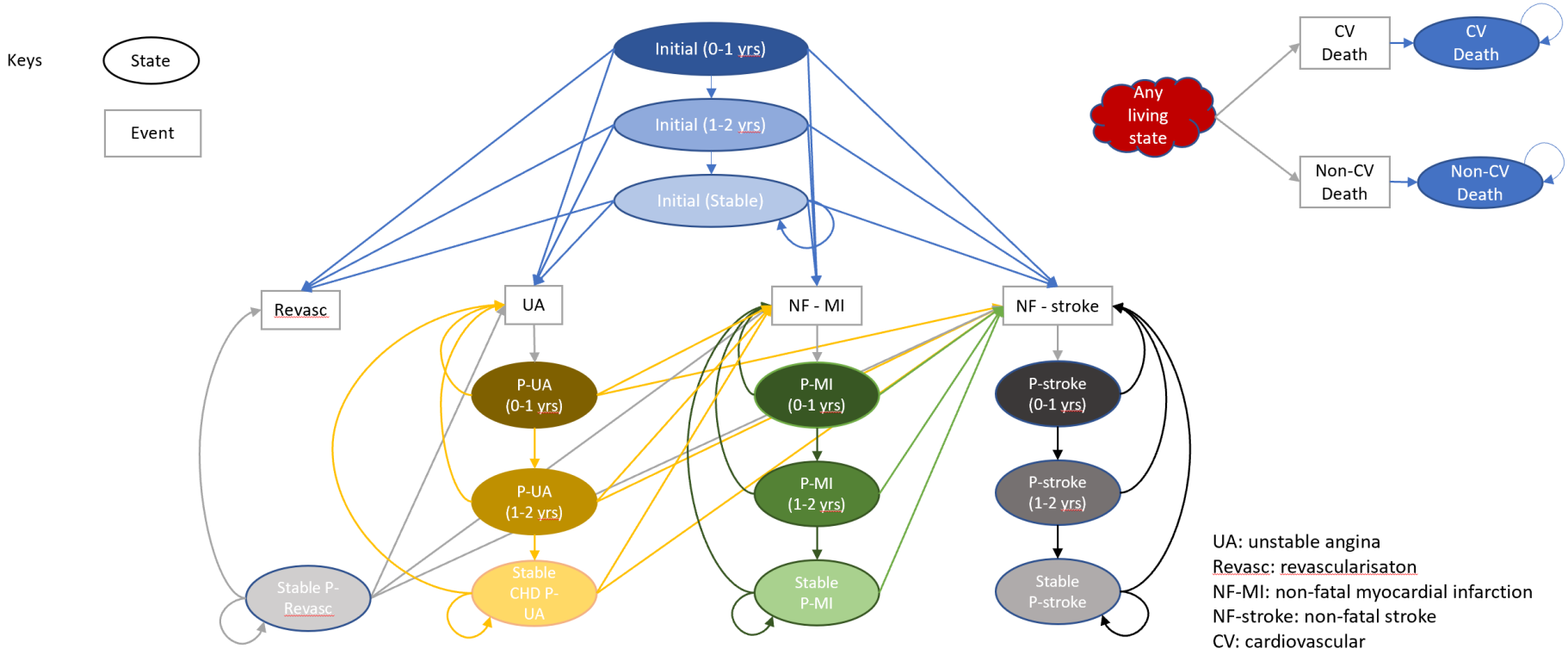
Event	Definition
Revascularisation	An elective revascularisation that is not the result of an ACS event
UA	Unstable angina with a hospitalisation
NF-MI	Non-fatal MI with a hospitalisation
NF-stroke	Non-fatal ischemic stroke with a hospitalisation
CV death	Death due to CV causes
Non-CV death	Death due to non-CV causes

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; NF, non-fatal; UA, unstable angina.

The model comprises 15 mutually exclusive discrete health states (Figure 60):

- 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.

Figure 60: Markov model schematic



Patients enter the model in one of three initial states based on time post-CV-event (Year 0–1 post-CV-event; Year 1–2 post-CV-event, and stable [Year 2+]). Patients can enter the model following a recent CV event ('Initial [0–1 years]', or 'Initial [1–2 years]' states), or not ('Initial [stable]' state). This distinction is made because the risk of further events is highest during the first year following a CV event (11). This is also reflected in the risks of further CV events in the non-fatal (NF)-CV health states (11).

Following movement to a post NF-CV event state, patients remain at risk of subsequent events (fatal or non-fatal). However, patients only formally move health states when a 'worse' event occurs – this is to avoid illogical outcomes, such as post-stroke patients with MI experiencing an improvement in HRQoL (as was observed in the model used in TA393 (11)). This event is then used for determination of HRQoL, resource use, and subsequent risk of fatal and non-fatal events. For example, a patient with 1–2 years' post-MI health who experiences a non-fatal stroke moves to this health state and experiences the HRQoL, costs, and increased risk of events associated with stroke. However if the same patient experiences unstable angina, they do not move health state, but instead experience a one-off cost and QALY decrement associated with unstable angina; the effects of milder non-fatal events within a given post non-fatal (NF)-CV event health state are captured as one-off costs and quality-adjusted life year (QALY) losses.

The overall model structure has also been validated through discussions with clinical experts during model development.

B.3.2.3 Baseline characteristics

The analysis considers the baseline characteristics of the cohort being analysed, including age, sex, prevalence of diabetes and average LDL-C at baseline (Table 63, Section B.3.3.1). Baseline characteristics are taken from the ORION clinical trials (Section B.2.3.6). Data for the primary and secondary prevention HeFH patients are taken from the relevant subgroups of ORION-9. Data for the ASCVD and PPER populations baseline characteristics are taken from the relevant subgroups in ORION-10 and -11.

Furthermore, the model also accounts for CV event history at baseline in patients with ASCVD. As per TA393 (11) a mixed cohort of patients is modelled including

patients with a history of MI or unstable angina (UA), other CHD, IS, or PAD. To capture this, the model is run for each cohort individually and the results are averaged over the sub-populations. Weights for each population have been taken from the taken from the CPRD analysis and are presented in Table 61. These weights have been assessed in a hierarchical manner, so patients with falling into multiple categories at baseline may only be counted once. The ordering of events is ACS 0-1, ACS 1-2, IS, Other CHD then PAD. Patients with ACS more than two years ago are included in the Other CHD population. Baseline characteristics in these sub-populations remain the same, however they are assigned different risks (Table 65).

Table 61: Definitions and weights for sub-populations

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

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

B.3.2.4 CV risks and risk adjustment

Baseline CV risks were taken from an analysis of the CPRD (Appendix L). This provides annual event risks for each model state, separately, for patients with and without diabetes. This analysis is discussed in Section B.3.3.2.

As the CPRD analysis provides an estimate of event risks with limited follow-up, further adjustment was required to incorporate increasing risks over time. An increase in risk of 3% each year is used as the base case for non-fatal CV events, and 5% for CV death, as per TA393 (11, 119). This adjustment is centred on the age in the population used to estimate the baseline event rate. Rates from CPRD are estimated separately for patients with and without diabetes (Section B.3.3.2) and then weighted according to the prevalence of diabetes in the population (Section B.3.3.1). Risks have not been adjusted for gender. While this is known to be a risk factor for CV events (119), as the risk data has been taken from CPRD it is assumed

to be reflective of the gender split in the UK population. The risk of non-CV mortality is adjusted for gender (Section B.3.3.6)

The baseline event risks from CPRD represent the risk of CV events in patients with existing ASCVD or FH but have not been assessed by severity of hypercholesterolaemia. To obtain event rates representative of SoC in the population of interest, baseline event rates were adjusted to reflect the average level of LDL-C in the population. Previous meta-analyses on the effect of lowering LDL-C on event rates have reported a log-linear relationship (120) and thus in line with previous submissions the following relationship is applied:

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

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.

This equation is applied to adjust the baseline risk of events to a population with a higher or lower serum LDL-C than the cohorts represented in the CPRD analysis at baseline.

As there are currently no outcomes data for inclisiran, the model uses reductions in LDL-C as an intermediate outcome which is then linked to reduction in CV events using the same relationship. A discussion of the RRs used is provided in Section B.3.3.4.

B.3.2.5 Discontinuation

Discontinuation of active therapy is not included in the base case but is included as a scenario analysis. Patients on active therapy (inclisiran, alirocumab or evolocumab) may discontinue in any cycle in the model and incur the costs and efficacy of the SoC arm. It is assumed that LDL-C returns to baseline levels immediately upon discontinuation.

Discontinuation of SoC is not included in the base-case analysis but is considered in a scenario analysis. In this analysis, patients discontinue statin therapy at the same rate in all arms of the model, and their underlying statin therapy and their level of LDL-C is adjusted to reflect this.

This approach was validated by clinical and health economics experts at an Advisory board (20).

B.3.2.6 Features of the economic analysis

Key features of the economic analysis are outlined in Table 62.

Table 62: Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TA393	TA394	Chosen values	Justification
Time horizon	Lifetime	Lifetime	Lifetime	In line with the reference case
Treatment effect waning?	No	No	No	No evidence of treatment effect waning Assumption consistent with other appraisals in hypercholesterolaemia
Source of utilities	Age-adjusted baseline disutilities based on Health Survey for England; from ODYSSEY for baseline, with multiplicative disutilities for CV events	Utility estimates were derived from NICE CG181 (9)	Age-adjusted baseline disutilities based on Health Survey for England	Health survey for England data was preferred in both TA393 (11) and TA394 (12)

Factor	Previous appraisals		Current appraisal	
	TA393	TA394	Chosen values	Justification
Source of costs	PSSRU for unit costs of H&SC; NHS reference costs for hospital procedures; BNF for drug acquisition costs	NHS drug tariff for SoC costs; NHS ref costs and PSSRU for monitoring costs; NICE CG181 and NHS ref costs for CV event costs.	PSSRU for drug administration costs; NHS reference costs for hospital procedures; BNF for drug acquisition costs	In line with the reference case

Abbreviations: BNF, British National Formulary; CG, clinical guideline; CV, cardiovascular; H&SC, health and social care; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; SoC, Standard-of-care; TA, technical appraisal.

B.3.2.7 Intervention technology and comparators

B.3.2.7.1 *Intervention*

The intervention considered is inclisiran (284 mg) administered as a subcutaneous injection on Day 1, Day 90, and then every 6 months 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 (Section B.2.3.1).

B.3.2.7.2 *Comparators*

Comparators within each population were selected based on current NICE recommendations (11) and TA394 (9, 12, 53). All populations were compared against SoC, represented by the placebo arms of the ORION clinical trial programme (Section B.2.3.5)[6], alirocumab in combination with SoC and evolocumab in combination with SoC.

Standard-of-care is considered to be a population-specific mix of maximally tolerated statin (including no statins in patients who are contraindicated or intolerant to statins) and other lipid-lowering therapy (including ezetimibe). 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

[6] Please note that in a population such as those contraindicated or intolerant to statins, SoC may already effectively be no treatment with lipid lowering therapies (SoC is population-specific).

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. Furthermore, the use of ezetimibe in clinical practice is low (4.1% of ASCVD patients in the CPRD analysis [Appendix L]). The cost of other lipid lowering therapies, with the exception of ezetimibe, have not been included in the economic analysis.

Bempedoic acid is not considered as a comparator as it is subject to an ongoing NICE appraisal and therefore cannot be considered part of established NHS practice, and no data are currently available to inform its inclusion in the model.

Non-lipid-lowering therapies commonly used as background therapy in these patient populations (e.g. angiotensin-converting-enzyme inhibitors [ACEi], angiotensin II receptor blockers [ARB], beta blockers, etc.) were not included in the analysis.

The composition of SoC by patient population (and sub-population) was taken from the ORION clinical trial programme (Section B.2.3.6). The distribution of background components of SoC are detailed in Table 76 (Section B.3.5.1).

B.3.3 Clinical parameters and variables

B.3.3.1 Patient characteristics

Baseline patient characteristics have been taken from the ORION clinical trial programme. Baseline data from ORION-9, -10 and -11 has been incorporated into the model and patient characteristics in the model are varied according to the population being modelled. This approach allows baseline characteristics to be varied consistently when patient populations are varied. Crucially, it allows for the calculation of the mean baseline LDL-C to be consistent with the specified minimum LDL-C. Baseline characteristics may also vary by diabetes status and treatment status at baseline.

Table 63: Baseline characteristics in each population

Population		Age	% female	% diabetes	LDL-C	Source
Secondary prevention	ASCVD and serum LDL-C ≥2.6 mmol/L	64.75	34%	38%	3.47	ORION-10 and -11 ASCVD patients
Primary prevention	PPER and serum LDL-C ≥2.6 mmol/L	62.28	54%	66%	4.02	ORION-11 PPER patients
	HeFH without ASCVD and serum LDL-C ≥2.6 mmol/L	52.36	58%	7%	4.09	ORION-9

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

B.3.3.2 Baseline risks

B.3.3.2.1 *CPRD analysis*

A retrospective, non-interventional, descriptive database analysis of patients with ASCVD and hypercholesterolemia, ASCVD-RE (termed PPER within this submission) with hypercholesterolaemia, or FH in England using the Clinical Practice Research Datalink (CPRD) linked to the Hospital Episode Statistics (HES) admitted patient care and Office of National Statistics (ONS) datasets was undertaken to estimate the twelve-month probabilities of MACE events and non-cardiovascular mortality associated with different baseline cardiovascular states. Within the ASCVD population, patients were further divided into subgroups based on their event history in order to capture the heterogeneity in event rates within the population.

Kaplan Meier survival analysis was used to estimate the probability of occurrence of each primary outcome (revascularisation, UA, non-fatal MI, non-fatal stroke, cardiovascular and non-cardiovascular death) within twelve months. Patients were followed from index date to date of event or censored at end of follow-up. 1-year survival probability was presented with the standard error.

The data for this study was retrieved from CPRD for patients who are HES eligible. CPRD is a longitudinal, anonymised research database derived from primary-care practices in the UK. Data within CPRD is collected as part of the day-to-day administration of the healthcare system. CPRD comprises two different though overlapping primary care datasets: CPRD GOLD and CPRD Aurum (Aurum). For this study Aurum was used which contains records on approximately 13 million currently registered patients (23% of the total English population) to maximise the study size. The primary-care dataset comprised data on demographics, diagnoses, prescriptions emanating in primary care, and other aspects of patient care. Approximately 70% of practices participate in a linkage scheme, by which their patient records are linked to other data sources, including the Hospital Episode Statistics (HES) dataset, which provides data on all inpatient and outpatient contacts occurring within National Health Service hospitals in England, and the Office for National Statistics (ONS) mortality dataset (The Office of National Statistics, 2019) which contains death registration data for all deaths in England and Wales.

Diagnostic information in the CPRD Aurum primary-care dataset is recorded using the SNOMED classification. HES inpatient and ONS mortality data are recorded using the ICD-10 classification.

Table 64: Population characteristics in the CPRD analysis

Population	Age	% female	% diabetes	LDL-C
ASCVD and serum LDL-C ≥2.6 mmol/L	68.77	45%	16%	3.47
HeFH without ASCVD and serum LDL-C ≥2.6 mmol/L	52.62	64%	2%	4.75
PPER and serum LDL-C ≥2.6 mmol/L	65.73	33%	15%	3.63

Among the populations considered within the CPRD analysis were ASCVD-RE patients, defined as per ORION-11. While these patients are at elevated risk of CV events, their risks are not as high as those for patients with ASCVD, thus rather than referring to them as risk-equivalent patients, their risks are used to inform the PPER population.

Further details are provided in Appendix L.

B.3.3.2.2 *Secondary prevention HeFH*

Results of the CPRD analysis for HeFH showed a number of inconsistent outcomes causing some level of confusion, and a questioning in the accuracy of the data analysed. CV event rates for the secondary prevention FH population were all lower than for the ASCVD population. The probability of MACE over 12 months was [redacted] vs. [redacted] for secondary prevention FH patients without diabetes and ASCVD patients without diabetes, respectively. In seeking an explanation, medical experts were approached to understand potential reasons for these inaccuracies. Their responses suggested that FH data from a CPRD data analysis should be interpreted with caution because there is often a coding issue where patients are inadvertently diagnosed as being FH. In UK clinical practice, patients are often coded with FH in CPRD databases without confirmation by genetic testing, which therefore leads to incorrect coding. It was also stated that patients are sometimes only suspected as being FH and never confirmed as FH, which again causes inaccuracies as it can lead to an underestimation of event rates in true HeFH cases.

An analysis was therefore run using data from the Morschladt et al. 2004 publication (121), used for the base-case analysis for secondary-prevention HeFH in TA393, which provides data on the CVD event and mortality risk in HeFH patients. This study had many advantages as it included patients with a confirmed diagnosis of HeFH. The limitation of this study is its relatively small sample size as it had only 131 secondary prevention patients, with 1105 years of follow-up. The study quotes the rate of all CV events (143 per 1000 patient years) and the rate of fatal CV events (12 per 1000 patient years), and also the distribution by type of CV events. The study reported the mean LDL-C for the secondary prevention group of 7.27 mmol/L, and that 1 year of statin treatment caused a 38% reduction in LDL-C levels.

Therefore, based on the above rationale and feedback from medical experts, the analysis based on Morschladt et al. has been used as the base case for the subgroup of patients with ASCVD and HeFH. The CPRD analyses will also be provided as a scenario analysis.

B.3.3.2.3 *Assigning risks to model health states*

Annual event probabilities from the CPRD analysis are assigned to health states based on the starting cohort being modelled and their event history upon reaching a given state. For example, the IS cohort starts in the initial stable state with the risks for the IS cohort in the CPRD analysis. Patients that experience a second IS event retain the event probabilities from the IS cohort (adjusted as described in Section B.3.2.4). Patients that go onto experience an acute coronary syndrome (ACS) event then have the event probabilities from the ‘stroke and ACS’ cohorts in the CPRD analysis. Further detail is provided in Table 65.

Table 65: Risk mapping from the CPRD analysis to the economic model

Health state	HeFH primary prevention	HeFH secondary prevention	ACS 0–1	ACS 1–2	Other CHD	IS	PAD	PPER	Very high risk of CVD†
Initial 0–1	N/A	N/A	ACS 0–1	N/A	N/A	N/A	N/A	N/A	N/A
Initial 1–2	N/A	N/A	ACS 1–2	ACS 1–2	N/A	N/A	N/A	N/A	N/A
Initial stable	HeFH primary prevention	HeFH secondary prevention	ACS stable	ACS stable	Other CHD	Stroke	PAD	ASCVD-RE	Very high risk CVD
Revasculari sation	Revasc	Revasc	Revasc and prior ACS	Revasc and prior ACS	Revasc	Revasc	Revasc and no prior ACS	Revasc	Revasc
UA 0–1	ACS 0–1	ACS 0–1	ACS 0–1	ACS 0–1	ACS 0–1	Stroke and ACS 0–1	ACS 0–1	ACS 0–1	Stroke and ACS 0–1
UA 1–2	ACS 1–2	ACS 1–2	ACS 1–2	ACS 1–2	ACS 1–2	Stroke and ACS 1–2	ACS 1–2	ACS 1–2	Stroke and ACS 1–2
UA stable	ACS stable	ACS stable	ACS stable	ACS stable	ACS stable	Stroke and ACS stable	ACS stable	ACS stable	Stroke and ACS stable
MI 0–1	ACS 0–1	ACS 0–1	ACS 0–1	ACS 0–1	ACS 0–1	Stroke and ACS 0–1	ACS 0–1	ACS 0–1	Stroke and ACS 0–1
MI 1–2	ACS 1–2	ACS 1–2	ACS 1–2	ACS 1–2	ACS 1–2	Stroke and ACS 1–2	ACS 1–2	ACS 1–2	Stroke and ACS 1–2
MI stable	ACS stable	ACS stable	ACS stable	ACS stable	ACS stable	Stroke and ACS stable	ACS stable	ACS stable	Stroke and ACS stable
IS 0–1	Stroke	Stroke	Stroke and ACS stable	Stroke and ACS stable	Stroke	Stroke	Stroke	Stroke	Stroke and ACS stable
IS 1–2	Stroke	Stroke	Stroke and ACS stable	Stroke and ACS stable	Stroke	Stroke	Stroke	Stroke	Stroke and ACS stable
IS stable	Stroke	Stroke	Stroke and ACS stable	Stroke and ACS stable	Stroke	Stroke	Stroke	Stroke	Stroke and ACS stable

†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).Abbreviations: ACS, acute coronary syndrome; HeFH, heterozygous familial hypercholesterolaemia; IS, ischaemic stroke; MI, myocardial infarction; N/A, not applicable; PAD, peripheral artery disease; PPER, primary prevention with elevated risk; UA, unstable angina.

B.3.3.3 Treatment efficacy

Treatment efficacy in reducing LDL-C has been taken from the NMA (Section B.2.9). The outcome selected for efficacy was the percent change in LDL-C at 24 weeks in all populations. Treatment efficacy was assumed constant across all baseline LDL-C categories following feedback received from medical experts at an advisory board run by Novartis in July 2020 (20). It was assumed that patients in the SoC arm do not experience any change in LDL-C. Efficacy has been estimated separately for patients with ASCVD or PPER and patients with HeFH, and all drugs are assumed to be used in addition to maximally tolerated statins. A scenario analysis for statin intolerant patients is also provided for the ASCVD and PPER populations. Table 66 and Table 67 present the base-case efficacy for the ASCVD and PPER, and HeFH populations, respectively. Table 68 presents the efficacy in stain intolerant patients for the ASCVD and PPER populations.

Table 66: Base-case efficacy for the ASCVD and PPER populations

Drug	% decrease in LDL-C	LCI	UCI
Alirocumab	[redacted]	[redacted]	[redacted]
Evolocumab	[redacted]	[redacted]	[redacted]
Inclisiran	[redacted]	[redacted]	[redacted]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LCI, lower confidence interval; PPER, primary prevention with elevated risk; UCI, upper confidence interval.

Table 67: Base-case efficacy for the HeFH population

Drug	% decrease in LDL-C	LCI	UCI
Alirocumab	[redacted]	[redacted]	[redacted]
Evolocumab	[redacted]	[redacted]	[redacted]
Inclisiran	[redacted]	[redacted]	[redacted]

Abbreviations: HeFH, heterozygous familial hypercholesterolemia; LCI, lower confidence interval; UCI, upper confidence interval.

Table 68: Efficacy in statin intolerant patients for the ASCVD and PPER populations

Drug	% decrease in LDL-C	LCI	UCI
Alirocumab	[redacted]	[redacted]	[redacted]
Evolocumab	[redacted]	[redacted]	[redacted]
Inclisiran	[redacted]	[redacted]	[redacted]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LCI, lower confidence interval; PPER, primary prevention with elevated risk; UCI, upper confidence interval.

While it is acknowledged that outcomes trials for alirocumab and evolocumab exist, which estimate a direct effect of treatment on the rate of CV events, the efficacy of these drugs has been estimated in the same manner as for inclisiran in order to present a consistent comparison.

B.3.3.4 Translating changes in LDL-C to changes in risk

The relationship between LDL-C and CV event risks was modelled using the Cholesterol Treatment Trialists (CTT) meta-analysis (122). The CTT analysis is based on 28 large-scale randomised controlled trials (RCTs) including ≥1,000 patients (n=186,854) with a treatment duration ≥2 years (122). Rate ratios for statin vs control at different levels of risk for major coronary events, strokes, coronary revascularisation and major vascular events per 1.0 mmol/L reduction of LDL-C were estimated.

The CTT analysis has been used in previous cost-effectiveness analyses for cholesterol lowering therapies (11) and has two key advantages over other available analyses. The specification of a scheduled treatment duration of at least 2 years is important, as it has been demonstrated that there is a link between exposure time and treatment effect, with observed RRs per mmol/L reduction in LDL-C being smaller in the first year of treatment (123). As such, including studies with a shorter duration may bias results. Additionally, while some analyses present only the impact on all major vascular events, the CTT analyses have presented RRs for individual outcomes relevant to the model, including CV death, MI, stroke and revascularisation.

The most recent analyses present two sets of results, one using all identified studies, and one excluding four studies that exclusively enrolled patients with heart failure or who were receiving renal dialysis, for whom statin treatment shows little or no benefit (122). The ORION studies exclude patients on renal dialysis or with New York Heart Association (NYHA) class IV heart failure and these patients would not be anticipated to benefit from cholesterol lowering therapy. As such the base-case analysis uses the values excluding these four studies.

Table 69 summarises the RRs applied in the model. The latest CTT analysis considers the impact on all strokes (122), however the model considers only IS, thus

a RR exclusively for IS has been used from a previous CTT analysis (124). This value has been used in previous economic models for cholesterol lowering therapies (11).

Table 69: 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

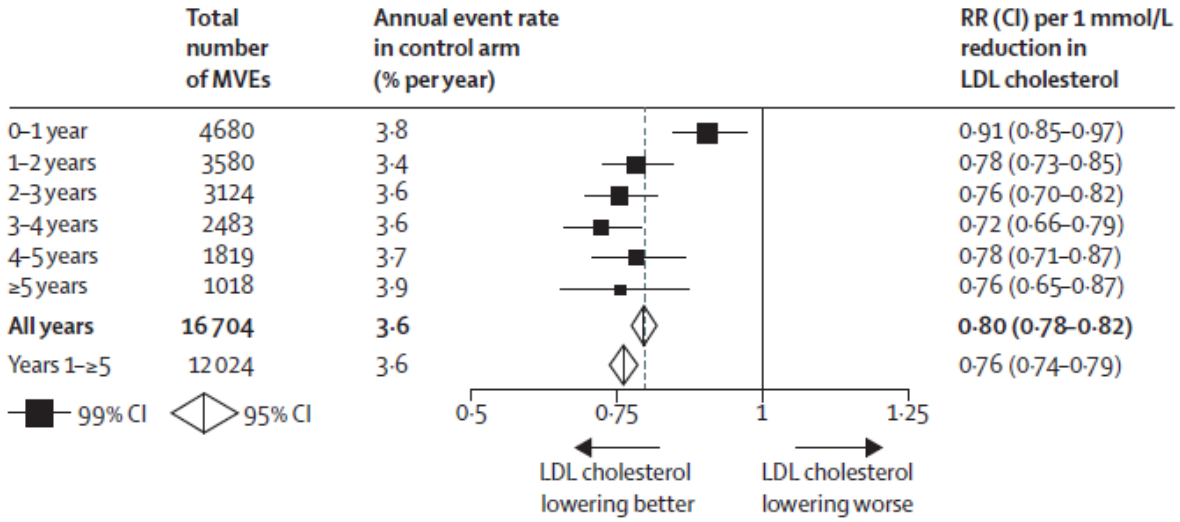
Event	RR per 1.0 mmol/L reduction in LDL-C	95% CI
Revascularisation	0.75	0.72, 0.78
NF-MI	0.73	0.70, 0.76
Stroke (any)	0.81	0.77, 0.86
Vascular death	0.84	0.80, 0.88
IS	0.79	0.74, 0.85

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

B.3.3.4.1 *Scenario analysis correcting for first year treatment effect*

Previous analyses have demonstrated that the impact of LDL-C lowering therapies is smaller in the first year of treatment (123). The RR for major vascular events was 0.8 per mmol/L reduction in LDL-C including all years, and reduced to the 0.76 when the first year was excluded. When extrapolating the impact of LDL-C lowering beyond 5 years, including the first year in the RR may under state the impact of LDL-C reductions. In order to assess the impact of this, a scenario analysis has been included in which a smaller RR is applied in the first year, with a larger RR each year thereafter. This is informed by the analysis from Collins et al, which demonstrates the impact on the RR for major vascular events of excluding the first year (123). The adjusted RRs were only applied when adjusting rates in the SoC arm to obtain rates for inclisiran and PCSK9 inhibitors and not when adjusting rates from the CPRD analysis to obtain event rates for SoC.

Figure 61: Proportional reduction in risks of major vascular events during each year of statin treatment



Abbreviations: CI, confidence interval; LDL, low density lipoprotein; MVE; major vascular event; RR, rate ratio.

In this scenario the RRs used to obtain event rates for inclisiran and PCSK9is are adjusted to remove the impact of the smaller effect in the first year according to the ratio between all years and Years 1 to 5, i.e. multiplied by 0.76/0.80. The effect in the first year is then reduced by 62.5% [1-(1-0.91)/(1-0.76)]. These rates are presented in Table 70.

Table 70: Effects on major coronary events, ischemic strokes, coronary revascularisation procedures, and major vascular events per 1.0 mmol/L reduction in LDL-C at different levels of risk used in the scenario analysis

Event	RR per 1.0 mmol/L reduction in LDL-C (Year 2+)
Revascularisation	0.713
NF-MI	0.694
IS	0.751
Vascular death	0.798

B.3.3.5 Discontinuation

B.3.3.5.1 *Discontinuation of inclisiran and PCSK9 inhibitors*

In scenarios considering discontinuation the rates have been taken from ORION-10 and -11 for patients with ASCVD or PPER and from ORION-9 for patients with HeFH. Across ORION-10 and -11 a total of 72 patients discontinued treatment with inclisiran when death is excluded as a reason for discontinuation, with a cumulative

exposure time of 2,281.4 years. This gives an annual discontinuation rate of 3.2%. In ORION-9, 6 patients discontinued inclisiran over 356.1 years of exposure, giving an annual discontinuation rate of 1.7%.

Discontinuation rates for alirocumab and evolocumab have been taken from the ODDYSEY Outcomes and FOURIER trials respectively. In ODDYSEY Outcomes 14.2% of patients (1,343/9,462) patients discontinued prematurely in the alirocumab arm. Only a median follow-up time of 2.8 years could be identified for the trial. Assuming this is the mean follow-up time gives an annual discontinuation rate of 5.7%. The discontinuation rate in FOURIER was 5.7% per year.

Two discontinuation scenarios are presented here (Table 71), the first using the calculated discontinuation rates for each drug and the second assuming that 5% of patients discontinue each year in all arms.

Table 71: Inclisiran and PCSK9 inhibitor discontinuation scenarios

Arm	Scenario 1	Scenario 2
Inclisiran (ASCVD & PPER)	3.2%	5%
Inclisiran (HeFH)	1.7%	5%
Alirocumab	5.1%	5%
Evolocumab	5.7%	5%

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; PPER, primary prevention with elevated risk.

B.3.3.5.2 *Discontinuation of statins*

A separate scenario considers the impact of patients discontinuing statin therapy. Patients discontinuing statin therapy revert to the LDL-C at baseline of a patient not taking statins, in effect raising the LDL-C level for the population and leading to higher event rates.

Data from ORION-10 and-11 were used for the ASCVD and PPER populations and data from ORION-9 was used to inform statin discontinuation rates for patient with HeFH. Across ORION-10 and -11, 49 of 2,902 patients receiving statins at baseline discontinued their statin therapy across 4,151 patient years of exposure, giving a statin discontinuation rate of 1.18% per year. In ORION-9, 4 of 433 patients on statin therapy at baseline discontinued their statins over 636.8 years of exposure, giving a statin discontinuation rate of 0.6% per year.

B.3.3.6 Non-CV mortality

Rates of non-CV mortality were taken from lifetables for England and Wales (125) which have then been adjusted to remove the proportion of deaths due to CV causes using cause-specific mortality data (126).

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality of life (HRQoL) data will not be available from the ORION programme at the time of launch.

B.3.4.2 Mapping

Mapping was not required as EQ-5D data are available in the public domain (Section B.3.4.5).

B.3.4.3 Health-related quality-of-life studies

B.3.4.3.1 *Identification of studies*

An SLR was conducted to identify HRQoL studies relevant to the decision problem from the published literature. A complete description of the search strategy is presented in Appendix H.

B.3.4.3.2 *Description of identified studies*

The SLR identified 214 studies that met the pre-defined inclusion criteria. A complete description of the identified studies is presented in Appendix H.

B.3.4.4 Adverse reactions

During the ORION Phase 3 clinical trial programme, TEAEs and TESAEs leading to study drug or study discontinuation were balanced between the inclisiran and placebo arms (Section B.2.10).

Injection site TEAEs occurred more frequently with inclisiran than placebo. However, all TEAEs at the injection site were localised, predominantly mild or occasionally moderate, transient, and resolved without sequelae. A pre-specified Medical Dictionary for Regulatory Activities (MedDRA) broad basket of terms of CV outcomes

showed numerically lower event rates in the inclisiran arm compared with placebo, and there were no clinically relevant differences in the TEAE profile of inclisiran compared with placebo for any of the safety subgroups or special populations studied.

The incidence of relevant TEAEs was included for inclisiran and comparators, and a disutility and/or cost was applied. For inclisiran and PCSK9 inhibitors, injection site reactions were considered a relevant TEAE. As SoC is common to all model treatment arms in the primary comparison, the effects of including adverse events associated with SoC on cost-effectiveness are expected to be minimal and are therefore excluded.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The utility values are informed by a study by Ara & Brazier (127) which estimates 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 are then derived by applying multipliers presented in Table 72, taken from TA393 (11). This approach was validated by clinical and health economics experts at an Advisory board (20).

Table 72: Baseline utility multipliers for each cohort

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 are applied when a patient experiences an event. These are presented in Table 73.

Table 73: Post-event utility multipliers

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 one-off QALY loss applied to patients experiencing an acute event in a more severe health state are calculated as the difference in utilities between Year 1 post-event and the stable post-stroke utility, regardless of the baseline health state.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

The costs per dose for evolocumab and alirocumab were taken from the British National Formulary (BNF) (Table 74) (128). List prices for evolocumab and alirocumab have been applied as the discounted prices are not publicly available.

Table 74: Unit costs and resource use for PCSK9 inhibitors

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 (128)
Alirocumab	75 or 150	1	168.00	75–150 mg every 2 weeks	BNF (128)

Abbreviation: BNF, British National Formulary.

Per-cycle costs for statins and ezetimibe (components of SoC) were included. Given that the costs of SoC are not expected to be a driver of cost-effectiveness (as they are applied in all arms of the model), a representative therapy was selected for each

statin intensity by selecting the most commonly used statin for each intensity in the ORION-11 clinical trial. Unit costs and resource use for each representative therapy were taken from the BNF (128), and the proportion of patients taking high, moderate or low intensity statins were based on those used at baseline in the relevant subgroup of the ORION clinical trial programme where available. As statins and ezetimibe are predominantly prescribed in primary care the drug tariff price has been used, as per the NICE reference case. Unit costs and resource use associated with ezetimibe and statin are presented in Table 75.

Table 75: Unit costs and resource use for SoC

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

Abbreviations: SoC, standard-of-care.

The composition of SoC by patient population is taken from the relevant clinical trials and presented in Table 76.

Table 76: Composition of SoC by patient population

Population	No LLT	High intensity statin	Moderate intensity statin	Low intensity statin	Ezetimibe	Other LLT	Source
ASCVD and serum LDL-C ≥2.6 mmol/L	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 ≥2.6 mmol/L	7%	72%	15%	2%	51%	4%	ORION-9
ASCVD and serum LDL-C ≥2.6 mmol/L	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 ≥2.6 mmol/L	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.

The cost of administration for inclisiran was assumed to be 10 minutes of nurse time, taken from the Unit Costs of Health and Social Care 2019 (129). Administration costs for alirocumab, evolocumab and SoC were assumed to be zero, given that the considered components are self-injected or oral therapies (Table 77). While alirocumab and evolocumab are self-administered, clinical input has indicated that the majority of patients receiving these treatments remain in secondary care in order to receive the patient-access scheme (PAS) price which is not available in primary care. While no additional administration costs have been considered, in clinical practice 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.

Table 77: Administration costs

Component	Cost (£)	Source
Administration of inclisiran	6.17	Unit Costs of Health and Social Care 2019 (129), page 118. Nurse (GP practice): £37 per hour, excluding qualifications.

Abbreviations: GP, general practitioner.

B.3.5.2 Health-state unit costs and resource use

A summary of the costs associated with each health state in the model can be found in Table 78. Acute costs for CV events have been taken from NHS reference costs with post-event costs being taken from CG181 and TA393. Costs in the stable states are applied beyond Year 3 as recommended by the evidence review group (ERG) in TA393. The cost per CV death was based on the cost per death in the alirocumab manufacturer submission to NICE of £1,174. Costs from CG181 and TA393 have been inflated from 2013/14 to 2018/19 prices using the HCHS pay and prices index (129). A systematic review of costs and resource use was carried out (Appendix I), however the sources used in previous appraisals have been retained for consistency.

Table 78: Cost of CV events split by year

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

Abbreviations: CV, cardiovascular; MI, myocardial infarction; N/A, not applicable; UA, unstable angina.

The cost of acute events was based on the weighted average cost of non-elective inpatient costs for MI, UA and stroke and the total HRG costs for revascularisation. The codes used to cost each are provided in Table 79.

Table 79: HRG codes used to cost acute events

Event	HRG codes
MI	EB10A-E
UA	EB13A-D
Stroke	AA35A-F
Revascularisation	ED26A-28C, YR10A-15C

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

B.3.5.3 Adverse reaction unit costs and resource use

Adverse events have not been incorporated into the model.

B.3.5.4 Miscellaneous unit costs and resource use

No additional costs were considered.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of base-case analysis inputs is provided in Table 80. A full description of the base-case inputs is provided in Appendix M.

Table 80: Summary of variables applied in the economic model

Variables	Source	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Baseline characteristics (Age, % male, % diabetes)	ORION clinical trial program	Varied in PSA according to distributions observed in relevant ORION populations	Table 63
Baseline LDL-C	ORION clinical trial program	Varied in PSA according to distributions observed in relevant ORION populations	Table 63
Cycle length	Annual	Not varied	Table 62
Discount rate (costs and outcomes)	3.5%	Not varied	Table 62
Treatment efficacy	From the NMA	Varied in PSA using the CODA	Table 66 Table 67
Baseline CV risks	From CPRD	Varied according to their standard errors using the beta distribution	Appendix L
Rate ratios for CV events per mmol/L reduction in LDL-C	CTT meta-analysis	Varied using 95% CIs assuming a normal distribution	Table 69
Baseline utility values and utility multipliers	Ara & Brazier 2010 (127)	Varied according to their standard errors using the beta distribution for baseline values and normal distribution for multipliers	Table 72 Table 73
Cost of PCSK9is	BNF	Not varied	Table 74
Distribution of SoC	ORION clinical trial program	Not varied	Table 76
Cost of SoC	BNF (Drug tariff)	Not varied	Table 75
Cost of CV events	NHS reference costs & CG181	Varied +/- 15%	Table 78

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.

B.3.6.2 Assumptions

A summary of assumptions is provided in Table 81.

Table 81: Assumptions

Assumption	Justification
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.
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 (130). 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.
Baseline data from the ORION clinical trials is representative of the UK ASCVD and HeFH populations	Table 63 and Table 64 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 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
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.

Assumption	Justification
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.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CPRD, Clinical Practice Research Datalink; CTT, Cholesterol Treatment Trialists; CV, cardiovascular; GP, general practitioner; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; PLD, patient level data; THIN, The Health Improvement Network.

B.3.7 Base-case results

Results for the base-case analysis in the ASCVD population, using the inclisiran commercial agreement price, are presented in Table 82. When compared to SoC, inclisiran produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in an ICER of [redacted]

Table 82: Base-case results ASCVD (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Results for the base-case analysis for the PPER population, using the inclisiran commercial agreement price, are presented in Table 83. When compared to SoC, inclisiran produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in an ICER of [redacted]. [redacted]

Table 83: Base-case results PPER (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Results for the base-case analysis in the primary prevention HeFH population, using the inclisiran commercial agreement price, are presented in Table 84. When compared to SoC, inclisiran produces an additional 0.298 QALYs with an incremental cost of [redacted], resulting in an ICER of [redacted]. [redacted]

Table 84: Base-case results primary prevention HeFH (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8 Sensitivity analyses

B.3.8.1 ASCVD

B.3.8.1.1 *Probabilistic sensitivity analysis*

Joint parameter uncertainty was tested through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. The results of the PSA (Table 85) were found to be congruent with the base-case results (Table 82). [redacted] Results were plotted on the cost-effectiveness plane (CEP; Figure 62) and a multiple cost-effectiveness acceptability curve (CEAC; Figure 63) was generated. [redacted]

Table 85: Results of probabilistic sensitivity analysis, ASCVD

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 62: Scatterplot of PSA results, ASCVD

Abbreviations: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 63: Multiple cost-effectiveness acceptability curve, ASCVD

Abbreviations: SoC, standard of care.

B.3.8.1.2 *Deterministic sensitivity analysis*

Parameter uncertainty was tested using deterministic sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range

determined by either the 95% CI, or ±15% where no estimates of precision were available. Upper and lower bounds used in deterministic sensitivity analysis are presented in Table 80. The results of deterministic sensitivity analysis are presented as a tornado diagram in Figure 64. [redacted]

Figure 64: Tornado diagram vs SoC, ASCVD

Abbreviations: SoC, standard of care.

B.3.8.2 Primary prevention with elevated risk

B.3.8.2.1 *Probabilistic sensitivity analysis*

Joint parameter uncertainty was tested through PSA, in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded. The results of the PSA (Table 86) were found to be congruent with the base-case results (Table 83). [redacted] Results were plotted on the CEP (Figure 65) and a multiple CEAC (Figure 66) was generated. [redacted]

Table 86: Results of probabilistic sensitivity analysis, PPER

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 65: Scatterplot of PSA results, PPER

Abbreviations: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 66: Multiple cost-effectiveness acceptability curve, PPER

Abbreviations:SoC, standard of care.

B.3.8.2.2 *Deterministic sensitivity analysis*

Parameter uncertainty was tested using deterministic sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range determined by either the 95% CI, or ±15% where no estimates of precision were available. Upper and lower bounds used in deterministic sensitivity analysis are presented in Table 80. The results of deterministic sensitivity analysis are presented as a tornado diagram in Figure 67. [redacted]

Figure 67: Tornado diagram vs SoC, PPER

[redacted]

Abbreviations: SoC , standard of care.

B.3.8.3 Primary prevention HeFH

B.3.8.3.1 *Probabilistic sensitivity analysis*

Joint parameter uncertainty was tested through PSA, in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded. The results of the PSA (Table 87) were found to be congruent with the base-case results (Table 82). [redacted] Results were plotted on the CEP (Figure 68) and a multiple CEAC (Figure 69) was generated. [redacted]

Table 87: Results of 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)
SoC	[redacted]	[redacted]	[redacted]	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 68: Scatterplot of PSA results, primary prevention HeFH

Abbreviations: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 69: Multiple cost-effectiveness acceptability curve, primary prevention HeFH

Abbreviations: SoC, standard of care.

B.3.8.3.2 *Deterministic sensitivity analysis*

Parameter uncertainty was tested using deterministic sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range

determined by either the 95% CI, or ±15% where no estimates of precision were available. Upper and lower bounds used in deterministic sensitivity analysis are presented in Table 80. The results of deterministic sensitivity analysis are presented as a tornado diagram in Figure 70. [redacted]

Figure 70: Tornado diagram vs SoC, primary prevention HeFH

Abbreviations: SoC, standard of care.

B.3.8.4 Scenario analysis

B.3.8.4.1 *Equal efficacy for inclisiran and PCSK9is*

The following analyses assume that PSCK9is have the same efficacy as inclisiran.

B.3.8.4.1.1 ASCVD

Table 88: Results in the ASCVD population assuming equivalent efficacy for inclisiran and PCSK9is

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.1.2 PPER

Table 89: Results for primary prevention patients with elevated risk assuming equivalent efficacy for inclisiran and PCSK9is

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.1.3 Primary prevention HeFH

Table 90: Results for the HeFH without ASCVD population assuming equivalent efficacy for inclisiran and PCSK9is

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.2 *Efficacy for inclisiran taken from the clinical trials*

Here the time-adjusted difference between inclisiran and placebo from the pooled efficacy dataset (51.43%) for ASCVD and PPER (Table 39) and from ORION-9 (43.19%) for HeFH (Figure 21) is used, rather than data from the NMA.

B.3.8.4.2.1 ASCVD

Table 91: Results in the ASCVD population using inclisiran efficacy from the ORION clinical trial programme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.2.2 PPER

Table 92: Results for primary prevention patients with elevated risk using inclisiran efficacy from the ORION clinical trial programme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.2.3 HeFH without ASCVD

Table 93: Results for the HeFH without ASCVD population using inclisiran efficacy from the ORION clinical trial programme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.3 *Adjusting rate ratios for CV events according to Collins et al*

The following scenario explores the impact of removing the first year of treatment from the calculation of rate ratios for CV events (Section B.3.3.4.1).

B.3.8.4.3.1 ASCVD

Table 94: Results in the ASCVD population adjusting the CV event RRs per mmol/L change in LDL-C to remove the impact of the first year

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.3.2 Primary prevention patients with elevated risk

Table 95 Results for primary prevention patients with elevated risk adjusting the CV event RRs per mmol/L change in LDL-C to remove the impact of the first year

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.3.3 Primary prevention HeFH

Table 96 Results for the HeFH without ASCVD population adjusting the CV event RRs per mmol/L change in LDL-C to remove the impact of the first year

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.4 *Including discontinuation of inclisiran and PCSK9is*

B.3.8.4.4.1 Scenario 1

This scenario explores the impact of discontinuation on cost-effectiveness, with discontinuation rates taken from the ORION trials for inclisiran, from ODDYSEY Outcomes for alirocumab and from FOURIER for evolocumab (Section B.3.3.5.1, Table 71).

B.3.8.4.4.1.1 ***ASCVD***

Table 97: Results in the ASCVD population including discontinuation: Scenario 1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[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.

B.3.8.4.4.1.2 ***Primary prevention patients with elevated risk***

Table 98 Results for primary prevention patients with elevated risk including discontinuation: Scenario 1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[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.

B.3.8.4.4.1.3 ***Primary prevention HeFH***

Table 99 Results for the primary prevention HeFH population including discontinuation: Scenario 1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[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.

B.3.8.4.4.2 Scenario 2

This scenario explores the impact of discontinuation on cost-effectiveness, assuming patients discontinue all treatments at the same rate (Section B.3.3.5.1, Table 71).

B.3.8.4.4.2.1 ***ASCVD***

Table 100: Results in the ASCVD population including discontinuation: Scenario 2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.4.2.2 ***Primary prevention patients with elevated risk***

Table 101 Results for primary prevention patients with elevated risk including discontinuation: Scenario 2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.4.2.3 ***Primary prevention HeFH***

Table 102 Results for the primary prevention HeFH population including discontinuation: Scenario 2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.5 *Including discontinuation of statin therapy*

This scenario explores the impact of discontinuation of statin therapy on cost-effectiveness, with discontinuation rates taken from the ORION trials (Section B.3.3.5.2). In the ASCVD and PPER populations the annual rate of discontinuation of statins is assumed to be 1.18% and is 0.6% for the primary prevention HeFH population.

B.3.8.4.5.1 ASCVD

Table 103: Results in the ASCVD population including discontinuation of underlying statin therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.5.2 Primary prevention patients with elevated risk

Table 104 Results for primary prevention patients with elevated risk including discontinuation of underlying statin therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.5.3 Primary prevention HeFH

Table 105 Results for the primary prevention HeFH population including discontinuation of underlying statin therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.6 *Assuming inclisiran has no impact on LDL-C until day 90*

The following scenario analyses assume that inclisiran has no impact on LDL-C until day 90.

B.3.8.4.6.1 ASCVD

Table 106: Results in the ASCVD population assuming no impact on LDL-C until day 90 for inclisiran

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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-car

B.3.8.4.6.2 Primary prevention patients with elevated risk

Table 107 Results for primary prevention patients with elevated risk assuming no impact on LDL-C until day 90 for inclisiran

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.4.6.3 Primary prevention HeFH

Table 108 Results for the primary prevention HeFH population assuming no impact on LDL-C until day 90 for inclisiran

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.8.5 Summary of sensitivity analyses results

The results of the PSA were highly congruent with the results of the base-case analysis. [redacted]

The most influential parameters identified in deterministic sensitivity analysis were the baseline rates of events, baseline utility multiplier and RRs per mmol/L reduction in LDL-C used to adjust the rates of CV events. The majority of scenario analyses do not demonstrate a significant change in the cost-effectiveness results. In the scenario including differential discontinuation rates for inclisiran and PCSK9is, inclisiran dominates alirocumab and evolocumab in all scenarios. This demonstrates the benefit of lower discontinuation rates achieved with inclisiran.

B.3.9 Subgroup analysis

B.3.9.1 ASCVD

B.3.9.1.1 *Patients with ASCVD and HeFH*

Table 109 presents the cost-effectiveness results for patients with a history of ASCVD and HeFH. Here the rate of CV events for this population have been taken from Morschladt et al. Efficacy has been informed by the HeFH base-case NMA. Results for this population are comparable to those for the overall ASCVD population. Patients in all arms gain more QALYs than in the overall ASCVD population, although this is because patients in the HeFH subgroup are on average 5 years younger than the overall ASCVD population. [redacted]

Table 109: Results for patients with ASCVD and HeFH, with event probabilities from Morschladt et al

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Table 110 presents results using event probabilities from the CPRD analysis for comparison. The event rates for HeFH with ASCVD from CPRD are lower than for the overall ASCVD population in CPRD or for HeFH in Morschladt et al, resulting in more LYs and QALYs for all arms and increasing the ICER for inclisiran to [redacted]

Table 110: Results for patients with ASCVD and HeFH, with event probabilities from CPRD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.9.1.2 *Severity of hypercholesterolemia*

Table 111 presents the results for patients with ASCVD and serum LDL-C ≥4.0 mmol/L, reflecting one of the populations in which alirocumab and evolocumab are recommended. Event risks for this population are higher, leading to a reduction in QALYs across all arms. Inclisiran remains the most cost-effective treatment option with and ICER of[redacted]

Table 111: Results for patients with ASCVD and serum LDL-C ≥4.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Table 112 presents the results for patients with very high risk of CVD and LDL-C ≥3.5 mmol/L. Inclisiran remains cost-effective, with an ICER of [redacted] Table 65 presents the mapped event risks for this subgroup, patients enter the model with the risk of patients with very high risk of CVD and LDL C concentration above 3.5 mmol/L in the CRPD analysis (Appendix L). No increase in event rates for subsequent states was applied.

Table 112: Results for patients with very high risk of CVD† and serum LDL-C ≥3.5mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).

B.3.9.1.3 *Statin intolerant*

Statin intolerant patients in ORION-10 & -11 had higher baseline LDL-C than the overall ASCVD (4.11mmol/L vs 3.47mmol/L). As a result of this they have higher event rates and the ICER for inclisiran is reduced to [redacted]

Table 113: Results for statin intolerant patients with ASCVD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.9.2 Primary prevention patients with elevated risk

B.3.9.2.1 *Statin intolerant*

Statin intolerant PPER patients in ORION-11 had higher baseline LDL-C than the overall PPER population (5.00 mmol/L vs 4.02 mmol/L). As a result of this they have higher event rates and the ICER for inclisiran is reduced to [redacted].

Table 114: Results for primary prevention patients with elevated risk who are intolerant to statins

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.9.3 Primary prevention HeFH

B.3.9.3.1 *Severity of hypercholesterolemia*

As severity of hypercholesterolemia increases, inclisiran becomes more cost-effective. [redacted]

Table 115: Results for patients with HeFH without ASCVD and serum LDL-C ≥3.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Table 116: Results for patients with HeFH without ASCVD and serum LDL-C ≥4.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Table 117: Results for patients with HeFH without ASCVD and serum LDL-C ≥5.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.9.3.2 *Statin intolerant*

Statin intolerant patients in ORION-9 had higher baseline LDL-C than the overall primary prevention HeFH population (5.03mmol/L vs 4.09mmol/L). As a result of this they have higher event rates and the ICER for inclisiran is reduced to [redacted]

Table 118: Results for patients with HeFH without ASCVD who are intolerant to statins

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

B.3.10 Validation

The model has been validated by modellers not involved in the development of the model and a version has been validated by an external company. The model was validated using standard procedures:

- Cell-by-cell checks of logic and consistency
- Logical check of model outputs
- Comparison of outputs to those from previous economic analyses

The model is based upon the model used for TA393, however the results are not directly comparable as there are several major differences between the analyses. Both the baseline rates of events and RRs used to adjust them according to LDL-C differ between the analyses. Additionally, the majority of the outcomes in TA393 were marked CIC and thus are not available for comparison.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Strengths and limitations

The primary strengths of this analysis are:

- The effectiveness of inclisiran in reducing LDL-C has been demonstrated in three large clinical trials representing the target populations. These trials are considered generalisable and the use of background therapies was representative of UK clinical practice.
- The model accounts for heterogeneity in the patient populations, both in terms of CV event history and time from the last event.
- The baseline event rates have been taken from a large UK primary care database, linked to hospital episodes data.
- The model structure and assumptions are based on a previously accepted economic evaluation (TA393).

This analysis relies on using changes in LDL-C observed in clinical trials, alongside rate ratios per mmol/L reduction in LDL-C for CV events to predict changes in outcomes since no CV outcomes data is available for inclisiran at this time. The rate ratios used to predict the changes in CV events have been taken from a large meta-analysis using patient-level data from over 100,000 patients. Although this represents a limitation, the relationship used (from the 2019 CTTC analysis (131)) represents the largest of such studies to investigate the relationship between LDL-C reduction and event risk reduction, and previous versions of this analysis have been used elsewhere in the economic evaluation of other therapies (131, 132).

Additional limitations include:

- Analysis of the CPRD database was not able to reliably inform the rates of CV events for secondary prevention HeFH, instead baseline rates are taken from a previously published analysis (121). However, this analysis is consistent with the approach taken in previous technology appraisals.

- The model uses the results of NMA in the absence of direct evidence. Whilst this analysis uses the best available evidence, the presence of heterogeneity across studies represents a limitation of the analysis.

B.3.11.2 Conclusions

This analysis has demonstrated that inclisiran is a highly cost-effective treatment for patients with ASCVD and LDL-C above 2.6 mmol/L, with an ICER of [redacted]. Additionally, inclisiran is a cost-effective treatment option for primary prevention patients with elevated risks and LDL-C above 2.6 mmol/L and for primary prevention patients with HeFH, with LDL-C above 4.0 mmol/L.

Appendices

The following appendices are included with the submission as separate documents:

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: CPRD analysis

Appendix M: Summary of model inputs

Appendix N: NMA report

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Responses to clarification questions

December 2020

File name	Version	Contains confidential information	Date
ID1647 inclisiran responses to clarification questions Fully Redacted	1	AiC/CiC	3rd December 2020

Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
Apo-B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
DSU	Decision Support Unit
EAS	European Atherosclerosis Society
EOS	End of study
ESC	European Society of Cardiology
FH	Familial hypercholesterolaemia
HDL-C	High density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LDL-C	Low density lipoprotein cholesterol
MACE	Major adverse cardiac event
MMRM	Mixed-effect models for repeated measures
MTD	Maximally tolerated dose
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PCSK9	Proprotein convertase subtilisin/kexin type 9
PMM	Pattern mixture model
PPER	Primary prevention with elevated risk
RE	Random effects
SD	Standard deviation
SoC	Standard-of-care

Section A: Clarification on effectiveness data

A1. Would all people suspected of hypercholesterolaemia or mixed dyslipidaemia receive genetic testing to determine whether they have homozygous or heterozygous mutations? If not, please clarify how this would be determined.

Within current clinical practice, not all people suspected of hypercholesterolaemia or mixed dyslipidaemia would receive genetic testing to determine whether they have homozygous or heterozygous mutations. Patients would only be suspected of FH if they have a very high total cholesterol (>7.5 mmol/L) or a relevant family history, after which the Simon Broome criteria or Dutch Lipid Clinic Network (DLCN) are often used in the UK to diagnose these patients, together with genetic testing (1). Having discussed this topic with medical experts, there is definitely a move towards using genetic testing for suspected FH patients more frequently. It is worth mentioning that there is increased likelihood that patients demonstrating characteristics of homozygous FH would receive genetic testing. We do not anticipate any impact on genetic testing with the availability of inclisiran.

A2. **Priority** Please explain why it has been assumed that a benefit from the Odyssey outcomes trial for alirocumab will generalise to inclisiran?

When referring to the Odyssey Outcomes trial for alirocumab in Section B.1.3.5 of the company submission, the emphasis was to support a threshold of ≥2.6 mmol/L. We acknowledge the trial design of Odyssey Outcomes is different to the clinical trial designs within the ORION programme and therefore the trials are not comparable, however the trial populations show some similarities in terms of LDL-C baseline level and background therapy. Additionally, NMA results showed that inclisiran had comparable efficacy to alirocumab and evolocumab across various hypercholesterolaemia patient populations. Therefore, we believe that the absolute benefit of inclisiran in the composite primary endpoint is more pronounced in patients with a baseline LDL-C level of ≥2.6 mmol/L.

A3. **Priority** The European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) guidelines which outline LDL-C targets <2.6 mmol/L for moderate, with <1.8 high risk and <1.4 in very high-risk patients (page 38 of

company submission). Would a threshold of ≥2.6 mmol/L potentially miss some high-risk cases?

The ESC/EAS guidelines outline target LDL-C levels that patients should aim to achieve, whereas the 2.6 mmol/L threshold referred to in the submission is a minimum threshold for eligibility to receive inclisiran, rather than a treatment target.

The key consideration should be that the ESC/EAS guidelines have created these thresholds as treatment targets that patients should achieve based on their risk. It should therefore be noted that high risk cases wouldn't necessarily be those with the most elevated LDL-C level as the risk is associated with a multitude of factors including documented cardiovascular disease, diabetes mellitus, FH, renal disease and very high levels of individual risk factors, to name a few (based on the ESC/EAS 2019 definition) (2).

From a clinical trial perspective, the LDL-C reduction seen across the ORION clinical trials was approximately 50%. When considering an LDL-C level of ≥2.6 mmol/L as a threshold, the treatment effect of an approximate 50% reduction is likely to lead to an absolute reduction of 1.3 mmol/L. This would therefore provide patients, even those with very high risk, the possibility of achieving the ESC/EAS guideline targets. When considering an appropriate threshold, extensive clinical trial data not only from the ORION clinical trial programme but also the other publications mentioned in Section B.1.3.5 of the company submission support a threshold of ≥2.6 mmol/L.

A4. Please clarify the following information in the decision problem table (Table 1, page 17 of company submission):

- For each population listed, does "maximally tolerated statins" include no statins where they are contraindicated or not tolerated?
- The subgroups for the 3 populations: atherosclerotic cardiovascular disease (ASCVD), primary prevention with elevated risk (PPER) and heterozygous familial hypercholesterolaemia (HeFH) without ASCVD, were defined by serum LDL-C thresholds. Please explain how these thresholds were selected. There are no thresholds listed for the primary prevention population at elevated risk (PPER group). Please clarify why.

Yes, maximally tolerated statins includes no statins where contraindicated/not tolerated, as no statin can represent a patient's maximally tolerated dose.

The 2.6 mmo/L threshold is applied across the three populations as described in the decision problem.

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 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.

Subgroup analyses were carried out at different thresholds that were selected to reflect the reimbursed populations for alirocumab and evolocumab in ASCVD and HeFH (3, 4). We did not carry out subgroup analyses for PPER at other thresholds as this population was not covered in the technology appraisal guidance.

A5. Please explain how maximally tolerated statin was defined. Was it defined based on information from patients' clinicians? Assuming maximally tolerated statin is strongly related to patient preference rather than a plateau in pharmacological effect, please explain whether it will impact on the outcomes that are observed following inclisiran administration.

As per the inclusion criteria of the ORION study protocols, patients that were receiving statins should have been receiving a maximally tolerated dose. This dose was defined as the maximum dose of statin that can be taken on a regular basis without intolerable AEs. Where subjects were not receiving a statin, there had to be documented evidence of an intolerance to all doses of at least two different statins.

Intolerance to any dose of any statin had to be documented as historical AEs attributed to the statin in question in the source documentation and on the medical history page of the electronic case report form.

Table 1 outlines the specific criteria used with reference to statin usage in the ORION clinical trial programme.

Table 1: Specific criteria relating to statin usage within the ORION clinical trial programme

There should be no plans at the time of screening and randomization to modify the dose of statin or other lipid lowering medication such as ezetimibe for the duration of the trial. Unless the background lipid lowering treatment exceptions described below are met, subjects must have been treated with one of the following highly effective statins at the specified daily doses and at a stable dose, preferably for 6 weeks but for at least 30 days, prior to screening for the study:

1. atorvastatin, 40 or 80 milligrams (mg) once a day;
2. rosuvastatin, 20 or 40 mg, once a day;
3. simvastatin 40 mg, once a day or, if a subject has been on that dose for >1 year, 80 mg, once a day.

Combination medications that contain atorvastatin, rosuvastatin, or simvastatin components described at the aforementioned doses will be permitted.

Background lipid lowering treatment exceptions

The following background lipid lowering treatment exceptions are permitted:

1. Lower doses of statins due to partial statin intolerance:
   Subjects may be on a lower dose of one of the highly effective statins described above if there is documented intolerance to any one of them (atorvastatin, rosuvastatin, or simvastatin) at the aforementioned doses. Intolerance to any dose of any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and electronic case report form (eCRF).
2. Regulatory limitations:
   Subjects may be on a lower dose of one of the highly effective statins described above if the highest locally approved dose for one of the stated statins is lower than those doses shown above (eg, in some countries, atorvastatin 20 mg, once a day, is the highest locally approved dose).
3. Alternative statins:
   Subjects may be treated with other statins (pravastatin, fluvastatin, pitavastatin, or lovastatin), different from the highly effective statins listed above, if there is documented intolerance to any two different highly effective statins (atorvastatin, rosuvastatin, simvastatin) at the lowest available daily dose for at least one of those highly effective statins. Intolerance to any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and eCRF.
4. No background statin therapy:
   Subjects may be enrolled who are only on non-statin lipid lowering therapy, if complete statin intolerance has been documented. Subjects with complete statin intolerance must be unable to tolerate at least two statins: one statin at the lowest available daily dose AND another statin at any dose. Intolerance to any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and eCRF. The sole exception, for which a subject may participate in the study with documentation of intolerance to only one statin, is a documented history of rhabdomyolysis attributed to that statin.

As described, patients needed to have documented evidence of any intolerances/adverse events to statins, which determined the type/dose of statin they would be on, if any. This was therefore a clinical judgement made physicians based

on their patients' experiences of intolerances/AEs, rather than a preference or plateau in pharmacological effect.

Concerning the impact on outcomes observed following inclisiran administration, we can see in the subgroup analyses of baseline statin treatment and intensity of statin treatment in Figures 18, 19 and 20 of the company submission (for ORION-9, -10 and -11, respectively) that there are still universal decreases in percentage change in LDL-C from baseline to Day 510. Expectedly, there is a slight difference in overall LDL-C reduction when comparing patients who were on statin treatment and those who were not, with the latter having a lower reduction. It should be noted however, that the patient numbers were low in this subgroup, which is reflective of current clinical practice (5). Similarly, the LDL-C percentage change was greater with those on high intensity statins compared with those not on high intensity statins. Interestingly, the subgroup analyses show that across all three trials the patients who were on any statin still managed 49.7%, 57.3% and 53.3% LDL-C percentage changes from baseline to Day 510 in ORION-9, 10 and 11, respectively.

A6. Regarding baseline LDL-C ≥2.6 mmol/L, the company referenced a clinical trial in its submission (reference 18 in the company submission). Please clarify whether that the trial included patients from the UK.

Upon review of the supplementary appendix of this reference, we can confirm that in this particular clinical trial there were 292 patients enrolled from the UK (6).

A7. In the decision problem, and section B.1.3.6.3 the company indicates that ezetimibe in addition to statins has a limited potency and results in smaller LDL-C reductions compared to other lipid lowering alternatives (20%), particularly in high risk groups.

- Please provide any data to support that ezetimibe with statins has lower reductions in LDL-C compared to other lipid lowering alternatives?

- Please explain why ezetimibe has been added as a standard of care comparator therapy in all arms, when it is so infrequently used (stated in decision table, page 18: 4.1% in ASCVD, 1.5% in PPER, 5.4% in HeFH).

Section B.1.3.6.3 of the company submission refers to the limited potency of ezetimibe plus other oral lipid-lowering therapies. Ezetimibe was compared with PCSK9 inhibitors in the ASCVD population in the following trials:

- LAPLACE-2 (7) for evolocumab vs ezetimibe
- ODYSSEY COMBO II (8) and ODYSSEY EAST (9) for alirocumab vs ezetimibe.

Using data from LAPLACE-2, wherein randomisation was stratified by background statin, n-weighted treatment group means and SDs were calculated for the percentage change in the LDL-C level from baseline to Week 12. Across all arms and stratifications in LAPLACE-2, the percent change was calculated to be [redacted] in the ezetimibe group and [redacted] in the evolocumab 140 mg group (3), for a between-group difference of [redacted].

In ODYSSEY COMBO II, the percentage change in the LDL-C level from baseline to Week 24 was –20.7 (SD 29.4)[a] in the ezetimibe group and –50.6 (SD 30.3)[a] in the alirocumab group, for a between-group difference of −29.8% (95% CI −34.4 to −25.3; p<0.0001) (8).

In ODYSSEY EAST, the percentage change in the LDL-C level from baseline to Week 12 was –20.3% (SD 28.8)[a] in the ezetimibe group and –56.0% (SD 30.1)[a] in the alirocumab group, for a between-group difference of −35.6% (95% CI −40.6 to −30.7; p<0.0001) (9).

The NMA results demonstrate that [redacted] (Table 2).

Table 2: % CFB in LDL-C at 24 weeks vs ezetimibe based on NMA

Intervention	Difference in % CFB [95% CrI]	Probability better than ezetimibe
ASCVD on MTD statin		
Inclisiran	[redacted]	[redacted]
Evolocumab	[redacted]	[redacted]

[a]SD converted from SE (reported in the publication) using the formula SD=SE*sqrt(N

Alirocumab	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; MTD, maximally tolerated dose.

Please see response to A14 onto why ezetimibe has been added as a standard of care comparator therapy.

A8. The company indicates that apheresis "is used very infrequently in England' (section B.1.3.5.5.), did the company find any actual data on "use" of apheresis in the UK?

We estimate that the percentage use of apheresis in England would be less than 0.05% of the ASCVD and primary prevention population. This is based on:

- The NHS Blood and Transplant department stating that their Therapeutic Apheresis services treat over 1,200 adults and children every year in England and North Wales (10)
    - This figure includes, but is not specific to, 'Low Density Lipid Removal', as it also includes 'Peripheral Blood Stem Cell Collection", "Lymphoctye Collection", "Therapeutic Plasma Exchange", "Red Cell Exchange", "Platelet Depletion", "White Cell Depletion" and "Extracorporeal Photopheresis". Given the small number of over 1,200 treated patients, this indicates how low the numbers would be specifically for Low Density Lipid removal.
    - The figure of 1,200 patients also includes children in whom inclisiran will not be licensed.
- There are an estimated 2.6 million adults in England with ASCVD or at elevated risk of developing ASCVD, with an LDL-C level of ≥2.6 mmol/L despite receiving statins and/or ezetimibe (11).

It should also be considered that NHS therapeutic apheresis services are only available in eight units across England and North Wales.

In addition to the above, as stated in our submission, apheresis is more frequently prescribed for patients with homozygous familial hypercholesterolaemia, who are outside the licensed population for inclisiran.

A9. Page 51 of the company submission: It is stated that the phase 3 trials altogether provided 3000 patient-years of data on inclisiran's safety and LDL-C lowering effect after 18 months of treatment. The concept of patient-years applies more to a dynamic population, which is not expected in a clinical trial. Please explain this?

We would be in agreement that presenting patient years of data in this manner is usually reserved for a dynamic population, and it therefore unusual for a clinical trial programme. From a company perspective, this figure has only been presented to show a conservative calculation of the number of patients treated with inclisiran over 18 months during the ORION phase 3 studies.

In total, 3,660 patients were treated with inclisiran across ORION-9, -10, and -11 (ITT population).

A10. There appears to be s some discrepancy in the population of ORION-9 with regards to patients with ASCVD. In Document B, ORION-9 study included only primary prevention population (i.e., patients with heterozygous familial hypercholesterolaemia (HeFH) and elevated LCL-C, i.e., those with no ASCVD), whereas Table 12 indicates that ORION-9 study included 132 patients with ASCDV. Please clarify this discrepancy.

Please see response to A12.

A11. Please clarify at what time point in ORION-9, ORION-10 study follow-up was major adverse cardiac event (MACE) measured? Please also clarify what the abbreviation 'EOS' stand for.

In ORION-9 and ORION-10, follow-up was measured until Day 540 for MACE, as per the total study duration. EOS is an abbreviation for 'end of study'.

A12. The company submission indicates throughout (e.g., Table 9, page 56) that ORION-9 included patients with HeFH and elevated LDL-C (i.e., ASCVD-RE primary prevention population). This suggests that there are no patients with ASCVD

(secondary prevention) in ORION-9 study. However, Table 12 (page 60 of the company submission) indicates that ORION-9 study actually included 132 (27.4%) patients with history of ASCVD. Please clarify this apparent discrepancy.

ORION-9 included HeFH patients but did not exclude secondary prevention HeFH patients (i.e. ASCVD); it included both primary and secondary prevention patients (only patients with MACE within 3 months prior to randomisation were excluded [company submission, Table 9, Page 56]). As mentioned above, 132 (27.4%) patients in ORION-9 had a history of ASCVD (company submission, Table 12, Page 61).

A13. Sub-group analyses, Figures 19-20 (pages 100-101 of the company submission) ORION-10/11 : The larger clinical benefit (% reduction in LDL-C) observed in subgroups of patients with lower baseline LDL (≤5.3 mmol/L vs. >5.3 mmol/L) in ORION-10/11 studies is in contrast with the company's assertion made in the decision problem (Table 1, page 17 of the company submission) that the treatment effect is expected to be greater in patients with a higher baseline LDL-C, (≥2.6 mmol/L) compared with patients with lower LDL-C (<2.6 mmol/L). Please clarify this discrepancy.

This 5.3 mmol/L cut-off does not represent anything we are familiar with. The subgroups presented in the forest plots in Figure 19 (ORION-10) and Figure 20 (ORION-11) used cut-offs of 2.46 mmol/L (95 mg/dL) and 2.51 mmol/L (97 mg/dL), respectively.

The apparent discrepancy is due to the difference between relative and absolute treatment effects. The relative efficacy of inclisiran versus placebo (in terms of percentage change in LDL-C from baseline to Day 510) was greater in subgroups of patients with lower baseline LDL-C levels (company submission, Figures 19–20, Pages 100–101). As mentioned on Page 100 of the company submission, this effect was driven by changes in the placebo arm, and has also been observed for comparator therapies (12). Feedback from UK clinical experts at a recent Novartis advisory board concluded that although there is no clear reason for this increase; a possible explanation could be that patients in the placebo arm with lower LDL-C levels were not very strict with medication (13). However, the text in the company submission, Table 1, Page 18 refers to absolute treatment effects. Patients with

baseline LDL-C ≥2.6 mmol/L have been shown to experience a greater absolute reduction in LDL-C following treatment, compared with patients with lower baseline LDL-C (6). This was also confirmed at the advisory board: "While there may be a smaller percentage change with a higher baseline LDL-C level, there is actually a bigger absolute reduction – this is clinically meaningful" (13).

A14. **Priority** Page 177 of the company submission states "Standard-of-care is considered to be a population-specific mix of maximally tolerated statin (including no statins in patients who are contraindicated or intolerant to statins) and other lipid-lowering therapy (including ezetimibe). Ezetimibe is included as part of SoC and therefore as part of background therapy in all arms. This is based on clinician input (13)…"

However, reference (20) Data on File [INC-DOF-001] page 10 states:

> *"The consensus from a clinical and health economics perspective is that as NICE guidelines treat ezetimibe as an active comparator, the NICE submission should ultimately reflect this.*
>
> *Answer: Ezetimibe should not be treated as the standard of care but should be considered an active comparator in the NICE submission"*
>
> Please confirm the full basis on which the company chose to include ezetimibe as part of the standard of care and provide complete reference to this advice.

The advice received at the Advisory board was based on the NICE draft scope and current treatment algorithm, which includes ezetimibe (14, 15). Ezetimibe has kept a very low usage in clinical practice despite having been approved by NICE for several years. Therefore, it is appropriate to consider it in a basket of therapies alongside statins. We understand its low usage is because of its marginal efficacy, which leads to patients becoming ineligible for PCSK9i's. However, we do acknowledge that ezetimibe is approved by NICE, and because it is also part of the permitted background therapy within the ORION trial programme we have included it as part of the SoC active comparator, rather than disregarding it.

Table 3 and Table 4 present the results of the cost-effectiveness analysis including ezetimibe+SoC as an active comparator, where SoC is defined as maximally

tolerated statin only. In this analysis the population has been restricted to those patients not taking ezetimibe at baseline, as ezetimibe is not a relevant comparator in patients who receive it as baseline. No analysis has been presented for the primary prevention HeFH population, as it was not possible to include ezetimibe in the NMA for this population.

Table 3: Cost-effectiveness results for the ASCVD population including ezetimibe as an active comparator

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Ezetimibe+SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SoC in this populations is limited to maximally tolerated statins.
Abbreviations: SoC, standard-of-care; LYG, life years gained; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

Table 4: Cost-effectiveness results for the PPER population including ezetimibe as an active comparator

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Ezetimibe+SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SoC in this populations is limited to maximally tolerated statins.
Abbreviations: SoC, standard-of-care; LYG, life years gained; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

A15. **Priority** In section B.2.4.6 (page 66 of the company submission), the paragraph "*The absolute change in LDL-C from 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 covariates*." Please clarify what these covariates were, and if they were the same as those used in the analysis of either of the co-primary endpoints.

For analyses of absolute change in LDL-C from baseline to Day 510 and percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B, and non-HDL-C by study (ORION-9, ORION-10, ORION-11 separately) an MMRM model was used that included treatment, visit, appropriate baseline value, and treatment-by-visit interaction. For the same analyses for pooled data from the three studies, the effects in the MMRM model included treatment, visit, study, baseline value, and treatment-by-visit interaction. These MMRM models were the same as used for the co-primary endpoint of LDL-C time adjusted percent change after Day 90 and up to Day 540. The other co-primary endpoint of percent change in LDL-C to Day 510 was analysed using an ANCOVA model that included treatment and baseline value only (and study for the pooled analyses).

A16. **Priority** Section B.2.6.1.3.2 (page 72 of the company submission) gives a between-group difference of -1.6 mmol/l, which is outside the range of the 95% CI provided. Please provide the corrected between-group difference.

This is a data entry error. The data in Section B.2.6.1.3.2 should read: 'The time-adjusted absolute change in LDL-C level from Day 90 to Day 540 using a control-based PMM was an increase of 0.1 mmol/l in the placebo group and a decrease of 1.5 mmol/l in the inclisiran group, for a between-group difference of −1.6 mmol/l (95% CI, −1.78 to −1.46 mmol/l; p<0.001).'

A17. The ERG could not locate a table presenting important inclusion/exclusion criteria and baseline patient characteristics (among them effect modifiers) across studies that were included in the network meta-analysis (NMA). Such a table would allow the ERG to qualitatively compare the distribution of potential effect modifiers between the compared direct comparisons to judge whether or not the transitivity assumption was violated in the NMA. Please either direct the ERG to where this table is or supply it.

The study design and patient characteristics identified as potential effect modifiers are summarised in Table 5, Table 6 and Table 7.

Table 5: Trial Characteristics

Trial name	Primary Publication	Disease Category	Trial design	N	# centres; location	Eligible interventions	LDL-C inclusion criteria	Treatment Duration (weeks)	Titration details	Run-in phase
ORION-1	Ray (2017)	ASCVD	Phase 2, multiple-ascending-dose trial	123	54; USA, Canada, Germany, Netherlands, UK	• Inclisiran 300mg • Placebo	LDL-C ≥70 mg/dL: ASCVD subjects LDL-C ≥100 mg/dL: ASCVD risk equivalent subjects	12.9	NR	NA
ORION-10	Ray (2020)	ASCVD	Phase 3, PC, DB	1,561	145; USA	• Inclisiran 300mg • Placebo	LDL-C ≥70 mg/dL	77.1	NR	NA
ORION-11	Ray (2020)	ASCVD	Phase 3, PC, DB	1,617	70; Czech Republic, Germany, Hungary, Poland, South Africa, Ukraine, UK	• Inclisiran 300mg • Placebo	LDL-C ≥70 mg/dL	77.1	NR	NA
ODYSSEY COMBO I	Kereiakes (2015)	ASCVD	Phase 3	316	76; USA	• Alirocumab 75/150 mg Q2W • Placebo	LDL-C ≥70 mg/dL: Patients with established CVD LDL-C ≥100 mg/dL: Patients with CHD risk equivalents	52	16.8%; Alirocumab dose increased to 150 mg Q2W at week 12	NA

Trial name	Primary Publication	Disease Category	Trial design	N	# centres; location	Eligible interventions	LDL-C inclusion criteria	Treatment Duration (weeks)	Titration details	Run-in phase
ODYSSEY COMBO II	Cannon (2015)	ASCVD	Phase 3	720	126; Canada, Denmark, France, Hungary, Israel, Russia, South Africa, South Korea, Ukraine, USA	• Alirocumab 75/150 mg Q2W • Ezetimibe 10 mg OD	LDL-C ≥70 mg/dL (1.8 mmol/L): Patients with a history of documented CVD LDL-C ≥100 mg/dL (2.6 mmol/L): Patients without history of documented CVD	104	18.4%; Alirocumab dose increased to 150 mg Q2W at week 12	NA
LAPLACE-2	Robinson (2014)	ASCVD	Phase 3	1,899	198; Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Italy, Netherlands, Russia, Spain, Sweden, Switzerland, UK, USA	• Evolocumab 140 mg Q2W • Ezetimibe 10 mg OD • Placebo	LDL-C ≥80 mg/dL: Patients with intensive statin at screening LDL-C ≥100mg/dL: Patients with non-intensive statin at screening LDL-C ≥150 mg/dL: Patients with no statin use at screening	12	NR	Patients tolerating placebo injection discontinued previous statin and ezetimibe use and were randomized
ODYSSEY CHOICE I	Robinson (2016)	ASCVD	Phase 3, PC, DB	547	105; USA, Canada, Hungary, UK, Bulgaria, Israel, Slovakia, Norway	• Alirocumab 75/150 mg Q2W • Placebo	LDL-C ≥70 mg/dL (1.8 mmol/L): Patients considered at very high CVD risk LDL-C ≥100 mg/dL (2.6 mmol/L): Patients considered at high or moderate CVD risk	48	19.7%; Alirocumab dose increased to 150 mg Q2W at Week 12 in a blinded fashion.	NA
NCT01288443	McKenney (2012)	ASCVD	Phase 2, DB, PG, PC	92	34; USA	• Alirocumab 150 mg Q2W • Placebo	LDL-C ≥100 mg/dL	12	NR	6-week run-in of atorvastatin

Trial name	Primary Publication	Disease Category	Trial design	N	# centres; location	Eligible interventions	LDL-C inclusion criteria	Treatment Duration (weeks)	Titration details	Run-in phase
ODYSSEY Long Term	Robinson (2015)	ASCVD	Phase 3, PC, DB, PG	2,341	320; 27 countries in North America, South America, Europe	• Alirocumab 150 mg Q2W • Placebo	LDL-C ≥70 mg/dL	78	NR	NA
LAPLACE-TIMI 57	Giugliano (2012)	ASCVD	Phase 2, DB, PC, dose-ranging trial	315	78; USA, Canada, Denmark, Hungary, Czech Republic	• Evolocumab 140 mg Q2W • Placebo	LDL-C ≥85 mg/dL (2.2 mmol/L)	12	NR	NA
FOURIER	Sabatine (2017)	ASCVD	Phase 3, DB, PC	27,564	1242; 49 countries worldwide	• Evolocumab 140 mg Q2W • Placebo	LDL-C ≥70 mg/dl	Median: 26 months	NR	NA
ODYSSEY EAST	Han (2020)	ASCVD	Phase 3, PG, DB	615	61; China, India, Thailand	• Alirocumab 75/150 mg Q2W • Ezetimibe 10 mg OD	LDL-C ≥70 mg/dL (1.8 mmol/L): Patients with a history of CV disease LDL-C ≥100 mg/dL (2.6 mmol/L): Patients without a history of CV disease (but with other risk factors)	24	18.8%; Alirocumab dose increased to 150 mg Q2W at week 12	NA
ODYSSEY KT	Koh (2018)	ASCVD	Phase 3, PC, DB, PG	199	27; South Korea, Taiwan	• Alirocumab 75/150 mg Q2W • Placebo	LDL-C ≥70 mg/dL: Patients with a history of documented CVD LDL-C ≥100 mg/dL: Patients without a history of documented CVD	24	9.5%; Alirocumab dose increased to 150 mg Q2W at week 12 in a blinded fashion	NA

Trial name	Primary Publication	Disease Category	Trial design	N	# centres; location	Eligible interventions	LDL-C inclusion criteria	Treatment Duration (weeks)	Titration details	Run-in phase
ODYSSEY OUTCOMES	Schwartz (2018)	ASCVD	Phase 3, PC, DB	18,924	1315; 57 countries worldwide	• Alirocumab 75/150 mg Q2W • Placebo	LDL-C ≥70 mg/dL	Median: 2.8 years	27.6%; alirocumab blinded increase to 150mg every 2 weeks at month 2 visit	2-16 weeks, maximum tolerated atorvastatin or rosuvastatin treatment was initiated, continued, or adjusted up to 2 weeks prior to the qualifying visit
ODYSSEY ALTERNATIVE	Moriarty (2015)	ASCVD; Statin intolerant	Phase 3, DB, PG	314	33; Austria, Canada, France, Israel, Italy, Norway, UK, USA	• Alirocumab 75/150 mg Q2W • Ezetimibe 10 mg OD • Placebo	LDL-C ≥70 mg/dL (1.8 mmol/L): Patients at very high risk LDL-C ≥100 mg/dL (2.6 mmol/L): Patients at moderate or high cardiovascular risk	24	49.5%; alirocumab dose was increased to 150 mg Q2W at week 12	4-week placebo run-in to exclude patients with non-statin–related muscle symptoms
ODYSSEY CHOICE II	Stroes (2016)	ASCVD; Statin intolerant	Phase 3, PC, DB	233	43; Australia, Belgium, Canada, Denmark, Netherlands, New Zealand, Spain, USA	• Alirocumab 75/150 mg Q2W • Placebo	LDL-C ≥70 mg/dL: Patients with very high cardiovascular risk LDL-C ≥100 mg/dL: Patients with high or moderate risk LDL-C ≥100 mg/dL and <160 mg/dL: Patients not fulfilling the SAMS definition, or who were being treated with diet alone	24	36%; alirocumab regimen changed to 150 mg Q2W at week 12 in a blinded fashion	NA

Trial name	Primary Publication	Disease Category	Trial design	N	# centres; location	Eligible interventions	LDL-C inclusion criteria	Treatment Duration (weeks)	Titration details	Run-in phase
ODYSSEY NIPPON	Teramoto (2019)	ASCVD; Statin intolerant	Phase 3, PC, DB, PG	163	30; Japan	• Alirocumab 150 mg Q2W • Placebo	Elevated LDL-C levels according to the JAS guidelines	12	22.7%; alirocumab 150 mg SC Q4W at Week 24	4-week run-in period on 5mg/day atorvastatin or non-statin LLT
GAUSS-2	Stroes (2014)	ASCVD; Statin intolerant	Phase 3, DB	307	58; USA, Australia, Belgium, Canada, Denmark, France, Germany, Hong Kong, Netherlands, Poland, South Africa, Spain, Switzerland, UK	• Evolocumab 140 mg Q2W • Ezetimibe 10 mg OD	Patients not at LDL-C goal for their NCEP-ATP III risk category	12	NR	NA
GAUSS-4	Koba (2020)	ASCVD; Statin intolerant	Phase 3, DB, PG	61	30; Japan	• Evolocumab 140 mg Q2W • Ezetimibe 10 mg OD	Patients must meet the LDL-C threshold based on their management category in the 2012 JAS Guidelines for the Diagnosis and Prevention of ASCVD in Japan	12	NR	NA
ORION-9	Raal (2020)	HeFH	Phase 3, PC, DB	482	46; USA, Canada, Czechia Denmark, Netherlands, South Africa, Spain, Sweden	• Inclisiran 300mg • Placebo	LDL-C ≥100 mg/dL at screening (history of untreated LDL-C of >190 mg/dL)	77.1	-	-
ODYSSEY Long Term	Robinson (2015)	HeFH	Phase 3, PC, DB, PG	415	320; 27 countries in North America, South America, Europe	• Alirocumab 150 mg Q2W • Placebo	LDL-C ≥70 mg/dL	78	-	-
RUTHERFORD-2	Raal (2015)	HeFH	Phase 3, DB, PC	331	39; Australia, Asia, Europe, New Zealand,	• Evolocumab 140 mg Q2W • Placebo	LDL-C ≥100 mg/dl	12	-	-

Trial name	Primary Publication	Disease Category	Trial design	N	# centres; location	Eligible interventions	LDL-C inclusion criteria	Treatment Duration (weeks)	Titration details	Run-in phase
					North America, South Africa					
ODYSSEY FH I	Kastelein (2015)	HeFH	Phase 3, PC, DB	486	89; 14 countries in North America and Europe	• Alirocumab 75/150 mg Q2W • Placebo	LDL-C ≥70 mg/dL (1.8 mmol/L): Secondary prevention LDL-C ≥100 mg/dL (2.6 mmol/L): Primary prevention	78	43.4%; alirocumab increased in blinded fashion to 150mg Q2W at Week 12	-
ODYSSEY FH II	Kastelein (2015)	HeFH	Phase 3, PC, DB	249	26; Czech Republic; Netherlands; Norway; UK	• Alirocumab 75/150 mg Q2W • Placebo	LDL-C ≥70 mg/dL (1.8 mmol/L): Secondary prevention LDL-C ≥100 mg/dL (2.6 mmol/L): Primary prevention	78	38.6%; alirocumab increased in blinded fashion to 150mg Q2W at Week 12	-
NCT01266876	Stein (2012)	HeFH	Phase 2, PC	46	16; Canada, USA	• Alirocumab 150 mg Q2W • Placebo	LDL-C ≥100 mg/dL (2.6 mmol/L)	12	-	6-week washout or statin stabilisation run-in for patients not on a stable statin dose (with or without ezetimibe) followed by the 1-week screening period
ODYSSEY HIGH FH	Ginsberg (2016)	**Disease Category**	Phase 3, PC, DB	107	33; Canada, USA, The Netherlands, Russia, South Africa	• Alirocumab 150 mg Q2W • Placebo	LDL-C ≥160 mg/dL	78	-	-

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DB, double-blind; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol; NR, not reported; PC, placebo controlled; PG, parallel-group; Q2W, every two weeks; Q4W, every four weeks

Table 6: Inclusion and Exclusion Criteria

Trial name	Primary Publication	Inclusion/ Exclusion Criteria	LDL-C inclusion criteria
ORION-1	Ray (2017)	**Inclusion:** Men and women 18 years of age or older; History of ASCVD or ASCVD-risk equivalents (T2D, FH, including subjects whose 10-year risk of a CV event assessed by Framingham Risk Score* or equivalent); Calculated GFR >30 mL/min by estimated glomerular filtration rate using standardized local clinical methodology; Subjects on statins were to be receiving a MTD (investigator's discretion); Subjects on lipid-lowering therapies (such as statin and/or ezetimibe) were to be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation **Exclusion:** Any use at any time of a monoclonal antibody drug targeting PCSK9; NYHA class II, III or IV heart failure or last known LVEF <30%; Major adverse cardiac event within 6 months prior to randomization; Any history of hemorrhagic stroke; Poorly controlled T2D, ie HbA1c >10.0% prior to randomization.	LDL-C ≥70 mg/dL: ASCVD subjects LDL-C ≥100 mg/dL: ASCVD risk equivalent subjects
ORION-10	Ray (2020)	**Inclusion:** Male or female participants ≥18 years of age; History of ASCVD (CHD, CVD, or PAD); Participants on statins should be receiving a MTD; Participants not receiving statins must have documented evidence of intolerance to all doses of at least 2 different statins; Subjects on LLT (such as a statin and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation. **Exclusion:** Major adverse CV event within 3 months prior to randomization; NYHA class IV heart failure; Uncontrolled cardiac arrhythmia; Uncontrolled severe hypertension; Active liver disease; Treatment with other investigational products or devices within 30 days or 5 half-lives of the screening visit, whichever is longer; Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9	LDL-C ≥70 mg/dL
ORION-11	Ray (2020)	**Inclusion:** Male or female participants ≥18 years of age; History of ASCVD (CHD, CVD, or PAD); Participants on statins should be receiving a MTD; Participants not receiving statins must have documented evidence of intolerance to all doses of at least 2 different statins; Subjects on LLT (such as a statin and/or ezetimibe) should be on a stable dose for ≥30 days before screening with no planned medication or dose change during study participation. **Exclusion:** Major adverse CV event within 3 months prior to randomization; NYHA class IV heart failure; Uncontrolled cardiac arrhythmia; Uncontrolled severe hypertension; Active liver disease; Treatment with other investigational products or devices within 30 days or 5 half-lives of the screening visit, whichever is longer; Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.	LDL-C ≥70 mg/dL
ODYSSEY COMBO I	Kereiakes (2015)	**Inclusion:** Aged ≥18 years; All patients were receiving a stable, maximally tolerated statin dose (defined as atorvastatin, 40-80 mg; rosuvastatin, 20-40 mg; or simvastatin, 80 mg daily; or lower doses provided the investigator had a documented reason for not using the higher dose, eg, intolerance and local practice) with or without other LLT (bile acid sequestrant, ezetimibe, niacin or omega-3 ≥1000 mg/day with stable dose ≥4 weeks; or fenofibrate with stable dose ≥6 weeks before enrollment) **Exclusion:** Known hypersensitivity to monoclonal antibody therapeutics, uncontrolled diabetes with HbA1c <8.5% or diagnosed within 3 months, clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins, blood pressure 160/100 mm Hg, major CV event within 3 months, NYHA class III or IV, heart failure within 12 months	LDL-C ≥70 mg/dL: Patients with established CVD LDL-C ≥100 mg/dL: Patients with CHD risk equivalents

Trial name	Primary Publication	Inclusion/ Exclusion Criteria	LDL-C inclusion criteria
ODYSSEY COMBO II	Cannon (2015)	**Inclusion:** Patients with hypercholesterolaemia and established CHD or CHD risk equivalents with LDL-C poorly controlled with a maximally tolerated daily dose of statin at stable dose for ≥ 4 weeks before screening. History of CHD included ≥1 of the following: Acute or silent MI, Unstable angina, Coronary revascularization procedure, Clinically significant CHD diagnosed by invasive or non-invasive testing. CHD risk equivalents: documented PAD, previous ischaemic stroke, CKD, known DM and ≥ 2 additional risk factor: History of hypertension, Documented history of ankle-brachial index ≤ 0.90, Documented history of microalbuminuria or macroalbuminuria OR dipstick urinalysis at screening visit (week –2) with > 2+ protein, Documented history of preproliferative or proliferative retinopathy or laser treatment for retinopathy; Known family history of premature CHD (CHD in father or brother < 55 years of age; CHD in mother or sister < 65 years of age) **Exclusion:** < 18 years of age; Fasting serum triglycerides > 4.5 mmol/L during the screening period; Currently on a statin that is not simvastatin, atorvastatin, or rosuvastatin; concomitant medication (ezetimibe, omega-3 fatty acid (at doses ≥ 1000 mg daily), nicotinic acid, bile acid-binding sequestrant, or red yeast rice products in the past 4 weeks prior to screening); Use of fibrates in the past 6 weeks	LDL-C ≥70 mg/dL (1.8 mmol/L): Patients with a history of documented CVD LDL-C ≥100 mg/dL (2.6 mmol/L): Patients without history of documented CVD
LAPLACE-2	Robinson (2014)	**Inclusion:** Aged 18-80 years old. Intensive statin use was defined as daily atorvastatin (40mg or greater), rosuvastatin (20mg or greater), simvastatin (80 mg), or any statin plus ezetimibe); fasting triglyceride levels of 400 mg/dL or less **Exclusion:** NHYA class III/ IV, or last known LEVF <30%; uncontrolled serious cardiac arrhythmia <=3months prior to randomisation; MI/ UA, PCI, CABG, or stroke <= 6 months prior to randomisation; planned cardiac surgery or revascularisation; type 1 DM; newly diagnosed or poorly controlled type 2 DM; high blood pressure; <= 6 weeks prior to screening: bile acid-sequestering resins, fibrates, red yeast rice, >200mg/day niacin, >1000mg/day omega-3 fatty acids; TSH < LLN or TSH >1.5× ULN; eGFR <30 mL/min/1.73m2; AST or ALT >2× ULN; CK >3× ULN; active infection; major hematologic, renal, metabolic, GI, or endocrine disruption; DVT or pulmonary embolism within 3 months; current or prior history of statin intolerance; requires maximal statin dosage, personal or family history of hereditary muscular disorders.	LDL-C ≥80 mg/dL: Patients with intensive statin at screening LDL-C ≥100mg/dL: Patients with non-intensive statin at screening LDL-C ≥150 mg/dL: Patients with no statin use at screening
ODYSSEY CHOICE I	Robinson (2016)	**Inclusion: V**ery-high CVD risk was defined as documented CHD or CHD risk equivalents (ischemic stroke, transient ischemic attack, carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, peripheral arterial disease, abdominal aortic aneurysm, renal artery stenosis, renal artery stent procedure, or T1DM or T2DM with target organ damage); high CVD risk was defined as no CHD/CVD but with a Systematic Coronary Risk Evaluation (SCORE) 10-year fatal CVD risk 5%, moderate CKD, T1DM or T2DM without target organ damage, or heterozygous familial hypercholesterolemia (by genetic or clinical criteria); moderate CVD risk was defined as a SCORE of between 1 and <5%; statin-associated muscle symptoms included the inability to tolerate at least two statins: one statin at the lowest daily starting dose and another statin at any dose, due to skeletal muscle-related symptoms; patients receiving concomitant statin were to receive stable daily doses (for at least 4 weeks) of rosuvastatin 20-40 mg, atorvastatin 40-80 mg, or simvastatin 80 mg, or MTD of one of these three statins; background treatment with LLTs other than statins was allowed for all patients, provided they had been on a stable dose for at least 4 weeks (6 weeks for fenofibrate) prior to study entry (excluding statins other than atorvastatin, rosuvastatin, or simvastatin, fibrates other than fenofibrate, and red yeast rice products).	LDL-C ≥70 mg/dL (1.8 mmol/L): Patients considered at very high CVD risk LDL-C ≥100 mg/dL (2.6 mmol/L): Patients considered at high or moderate CVD risk

Trial name	Primary Publication	Inclusion/ Exclusion Criteria	LDL-C inclusion criteria
		Exclusion: Patients with homozygous FH; currently taking a statin that is not atorvastatin, rosuvastatin or simvastatin; use of fibrates other than fenofibrate within 6 weeks of screening; use of allowed LLTs not at a stable dose/regimen for at least 4 weeks prior to screening; uncontrolled hyperthyroidism; uncontrolled blood pressure; recent MI, unstable angina leading to hospitalisation, PCI, CABG, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularisation, endovascular procedure or surgical intervention for peripheral vascular disease; planning to undergo scheduled PCI, CABG, or carotid or peripheral revascularisation during the study; known history of haemorrhagic stroke; history of NYHA Class III or IV heart failure within 12 months prior to the screening visit; newly diagnosed diabetes or poorly controlled diabetes (HbA1c >9% at the screening visit); previously treated with at least one dose of alirocumab or other PCSK9 monoclonal antibody in other clinical studies	
NCT01288443	McKenney (2012)	**Inclusion:** Eligible subjects were men and non-pregnant, non-lactating women age 18 to 75 years (inclusive) **Exclusion:** Drug-naive patients or patients either receiving LLT other than atorvastatin or not on a stable dose of atorvastatin 10, 20, or 40 mg daily for ≥6 weeks were eligible, provided that they met the inclusion criteria after discontinuing all other lipid-lowering therapy and completing a 6-week run-in of atorvastatin 10, 20, or 40 mg daily; T1D or T2D requiring insulin, or with HbA1c ≥ 8.5%; blood pressure >150/95 mm Hg; a history of major coronary event within 6 months of screening; a history of class II to IV heart failure	LDL-C ≥100 mg/dL
ODYSSEY Long Term	Robinson (2015)	**Inclusion:** Either A or B below and who were not adequately controlled with their lipid-modifying therapy: A) Participants with HeFH with or without established CHD or CHD risk equivalents OR B) Participants with hypercholesterolemia together with established CHD or CHD risk equivalents. **Exclusion**: Age <18 years	LDL-C ≥70 mg/dL
LAPLACE-TIMI 57	Giugliano (2012)	**Inclusion:** Male or female ≥ 18 to ≤ 80 years of age; On an approved statin, with or without ezetimibe, with stable dose(s) for at least 4 weeks **Exclusion:** NYHA Class III/IV heart failure or last known LVEF <30%; Serious cardiac arrhythmia within 3 months poorly controlled with medication; MI/unstable angina, PCI, CABG, stroke, DVT/PE within 3 months; planned surgery or PCI; SBP >160 mmHg and/or DBP >100 mmHg; T1DM; newly diagnosed or poorly-controlled T2DM (HbA1c ≥ 8.5%)	LDL-C ≥85 mg/dL (2.2 mmol/L)
FOURIER	Sabatine (2017)	**Inclusion:** Male or female ≥ 40 to ≤ 85 years of age at signing of informed consent; History of clinically evident CVD as evidenced by ANY of the following: diagnosis of MI, diagnosis of non-haemorrhagic stroke, symptomatic PAD; At least 1 major risk factor or at least 2 minor risk factors below: Major Risk Factors (1 Required):diabetes (type 1 or type 2); age ≥ 65 years at randomization (and ≤ 85 years at time of informed consent); MI or non-haemorrhagic stroke within 6 months of screening; additional diagnosis of myocardial infarction or non-haemorrhagic stroke excluding qualifying MI or non-haemorrhagic stroke; current daily cigarette smoking; history of symptomatic PAD	LDL-C ≥70 mg/dl

Trial name	Primary Publication	Inclusion/ Exclusion Criteria	LDL-C inclusion criteria
		Minor Risk Factors (2 Required): history of non-MI related coronary revascularization; residual CAD with ≥ 40% stenosis in ≥ 2 large vessels; Most recent HDL-C < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women by central laboratory before randomization; Most recent hsCRP > 2.0 mg/L by central laboratory before randomization; Most recent LDL-C ≥ 130 mg/dL (3.4 mmol/L) or non-HDL-C ≥ 160 mg/dL (4.1 mmol/L) by central laboratory before randomization; Metabolic syndrome; Most recent fasting LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L) or non-HDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) by central laboratory during screening after ≥ 2 weeks of stable lipid lowering therapy; Most recent fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) by central laboratory before randomization **Exclusion:** Subject must not be randomized within 4 weeks of their most recent MI or stroke; NYHA class III or IV, or last known left ventricular ejection fraction < 30%; Known haemorrhagic stroke at any time; Uncontrolled or recurrent ventricular tachycardia; Planned or expected cardiac surgery or revascularization within 3 months after randomization Uncontrolled hypertension defined as sitting SBP > 180 mmHg or DBP > 110 mmHg; Severe renal dysfunction, defined as an eGFR < 20 mL/min/1.73m2 at final screening; Active liver disease or hepatic dysfunction,	
ODYSSEY EAST	Han (2020)	**Inclusion:** 'Patients with hypercholesterolemia and established CHD or CHD risk equivalents who were not adequately controlled with a maximally tolerated daily dose of statin at a stable dose for at least 4 wk before the screening visit (see Supplemental Table 1). Patients with a history of CV disease (defined as CHD or CHD risk equivalents) were included if their LDL-C levels were aligned with the inclusion criteria for LDL-C. **Exclusion:** Patients without established CHD or CHD risk equivalents; History of an MI, unstable angina leading to hospitalization, CABG, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 3 mo before the screening visit (week -3, V1); History of New York Heart Association Class III or IV heart failure within the past 12 mo.	LDL-C ≥70 mg/dL (1.8 mmol/L): Patients with a history of CV disease LDL-C ≥100 mg/dL (2.6 mmol/L): Patients without a history of CV disease (but with other risk factors)
ODYSSEY KT	Koh (2018)	**Inclusion:** The study enrolled patients (aged ≥18 years) with high CV risk (defined as history of CV disease (CVD), moderate chronic kidney disease, or diabetes with multiple risk factors) who had inadequately controlled hypercholesterolemia (defined as LDL-C ≥70 mg/dL in patients with a history of documented CVD, or LDL-C ≥100 mg/dL in patients without such history) on maximally tolerated statin therapy (defined as atorvastatin 40 to 80 mg daily, rosuvastatin 20 mg daily, or simvastatin 40 mg daily) at a stable dose for at least 4 weeks before screening. **Exclusion:** Patients were not eligible if they were receiving statins other than atorvastatin, rosuvastatin, or simvastatin; fibrates other than fenofibrate; or red yeast rice products	LDL-C ≥70 mg/dL: Patients with a history of documented CVD LDL-C ≥100 mg/dL: Patients without a history of documented CVD

Trial name	Primary Publication	Inclusion/ Exclusion Criteria	LDL-C inclusion criteria
ODYSSEY OUTCOMES	Schwartz (2018)	**Inclusion:** Hospitalization for acute coronary syndrome, defined by symptoms of myocardial ischemia with an unstable pattern, occurring at rest or with minimal exertion, within 72 hours of an unscheduled hospital admission due to presumed or proven obstructive coronary disease and at least one of the following: Elevated cardiac biomarkers; Resting electrocardiographic changes consistent with ischemia or infarction, plus additional evidence of obstructive coronary disease from regional wall motion or perfusion abnormality; 70% or more epicardial coronary stenosis by angiography, or need for coronary revascularization procedure. Lipid levels inadequately controlled by atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg daily, or the maximum tolerated dose of one of these agents. **Exclusion:** Age less than 40 years; Qualifying index ACS event less than 4 weeks or more than 52 weeks before randomization; Uncontrolled hypertension (greater than 180 mm Hg systolic and/or greater than 110 mm Hg diastolic at randomization visit); New York Heart Association class III or IV congestive heart failure persisting despite treatment or left ventricular ejection fraction less than 25% if measured; History of hemorrhagic stroke; Recurrent acute coronary syndrome event within 2 weeks prior to randomization visit; Coronary revascularization procedure performed within 2 weeks prior to randomization visit or planned after randomization	LDL-C ≥70 mg/dL
ODYSSEY ALTERNATIVE	Moriarty (2015)	**Inclusion:** The population comprised patients (≥18 years) with primary hypercholesterolemia, at moderate or high cardiovascular risk. **Exclusion:** Newly diagnosed (within 3 months prior to randomization) diabetes mellitus or poorly controlled diabetes (glycated hemoglobin [HbA1c] >9%) History of New York Heart Association Class III or IV heart failure within the past 12 months Known history of hemorrhagic stroke	LDL-C ≥70 mg/dL (1.8 mmol/L): Patients at very high risk LDL-C ≥100 mg/dL (2.6 mmol/L): Patients at moderate or high cardiovascular risk
ODYSSEY CHOICE II	Stroes (2016)	**Inclusion:** 1. Adults ≥18 years of age with hypercholesterolemia receiving fenofibrate or ezetimibe or diet alone. 2. Only patients not receiving a statin were eligible, which corresponded to patients who (a) had SAMS (which was defined as statin intolerance in the protocol) with moderate, high, or very high cardiovascular risk or (b) were not receiving a statin but who did not fulfill the SAMS definition: only patients at moderate cardiovascular risk were included in this stratum. **Exclusion:** Patients with a 10-year fatal CVD risk SCORE <1% (ESC/EAS 2011) at the screening visit (Week –3, Visit 1); Patients newly diagnosed (within 3 months prior to randomization visit [Week 0]) or poorly controlled (HbA1c >9%) diabetes; Patients with history of New York Heart Association Appendix B Class III or IV heart failure within the past 12 months; Patients with history of a myocardial infarction, unstable angina leading to hospitalization, CABG, PCI, uncontrolled cardiac arrhythmia, carotid	LDL-C ≥70 mg/dL: Patients with very high cardiovascular risk LDL-C ≥100 mg/dL: Patients with high or moderate risk LDL-C ≥100 mg/dL and <160 mg/dL: Patients not fulfilling the SAMS definition, or who were being

Trial name	Primary Publication	Inclusion/ Exclusion Criteria	LDL-C inclusion criteria
		surgery or stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit (Week –3, Visit 1)	treated with diet alone
ODYSSEY NIPPON	Teramoto (2019)	**Inclusion:** Heterozygous familial hypercholesterolemia (heFH) or non-familial hypercholesterolemia (non-FH), were on the lowest-strength dose of atorvastatin or were receiving a non-statin therapy, and had not achieved recommended LDL-C levels Patients with non-FH were to have a history of documented coronary heart disease, or a history of diseases or other risk factors classified by the JAS as primary prevention category III (i.e. ischemic stroke, peripheral artery disease, diabetes mellitus, or chronic kidney disease) **Exclusion:** NR	Elevated LDL-C levels according to the JAS guidelines
GAUSS-2	Stroes (2014)	**Inclusion:** Patients aged 18 to 80 years not on a statin or were able to tolerate only a low-dose statin. **Exclusion:** Cardiovascular NYHA class III–IV heart failure or last known LVEF <30%; uncontrolled serious cardiac arrhythmia, defined as recurrent and highly symptomatic VT, AF with rapid ventricular response, or SVT that are not controlled by medications, within 3 months prior to randomization; MI, UA, PCI, CABG, or stroke within 3 months prior to randomization; Planned cardiac surgery or revascularization; DM (including Type 1 DM, Type 2 DM that is poorly controlled (HbA1c >8.5%) or newly diagnosed within 6 months before randomization)	Patients not at LDL-C goal for their NCEP-ATP III risk category
GAUSS-4	Koba (2020)	**Inclusion:** Age 20–80 years and Japanese by self-identification, for whom at least two statins failed because of myalgia, myositis or rhabdomyolysis. **Exclusion:** moderate to severe heart failure; uncontrolled cardiac arrhythmia; symptomatic coronary artery disease within 3 months before screening; recently diagnosed or poorly controlled diabetes, hypertension, or hyper-/hypothyroidism; known active infection or major hematologic, renal, hepatic, metabolic, gastrointestinal, or endocrine dysfunction; systemic steroid use; pregnancy or lactation; and previous exposure to any PCSK9 inhibitor.	Patients must meet the LDL-C threshold based on their management category in the 2012 JAS Guidelines for the Diagnosis and Prevention of ASCVD in Japan
ORION-9	Raal (2020)	**Inclusion:** '- HeFH by genetic testing and/or a documented history of untreated LDL-C of >190 mg/dL -History of familial hypercholesterolemia, elevated cholesterol or early heart disease that may indicate familial hypercholesterolemia -Receiving a maximally tolerated dose of statin or documented evidence of intolerance to all doses of at least 2 different statins **Exclusion:** NR	LDL-C ≥100 mg/dL at screening (history of untreated LDL-C of >190 mg/dL)

Trial name	Primary Publication	Inclusion/ Exclusion Criteria	LDL-C inclusion criteria
ODYSSEY Long Term	Robinson (2015)	**Inclusion:** Either A or B below and who were not adequately controlled with their lipid-modifying therapy: A) Participants with heterozygous familial hypercholesterolemia (heFH) with or without established coronary heart disease (CHD) or CHD risk equivalents OR B) Participants with hypercholesterolemia together with established CHD or CHD risk equivalents. **Exclusion:** Age < 18 years; LDL-C <70 mg/dL (< 1.81 mmol/L); Fasting serum triglycerides > 400 mg/dL (>4.52 mmol/L)	LDL-C ≥70 mg/dL
RUTHERFORD-2	Raal (2015)	**Inclusion:** -Diagnosis of HeFH using Simon Broome Register Group -On an approved statin with or without ezetimbe, with stable dose(s) for at least 4 weeks **Exclusion:** -HoFH -heart failure of NYHFA class III or IV or left ventricular ejection fraction <30% -Any acute or unstable cardiac event with planned intervention within 3 months of randomization -T1DM or newly diagnosed or poorly controlled (hemoglobin A1c>8.5%) T2DM	LDL-C ≥100 mg/dl
ODYSSEY FH I	Kastelein (2015)	**Inclusion:** HeFH patients who are not adequately controlled with a maximally tolerated stable daily dose of statin for at least 4 weeks prior to screening visit, with or without other LLT **Exclusion** -Known history of homozygous FH -History of documented CVD and LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit -Without history of documented CVD and LDL-C <100 mg/dL (<2.59 mmol/L) at the screening visit	LDL-C ≥70 mg/dL (1.8 mmol/L): Secondary prevention LDL-C ≥100 mg/dL (2.6 mmol/L): Primary prevention
ODYSSEY FH II	Kastelein (2015)	**Inclusion:** HeFH patients who are not adequately controlled with a maximally tolerated stable daily dose of statin for at least 4 weeks prior to screening visit, with or without other LLT **Exclusion:** -Known history of homozygous FH -History of documented CVD and LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit -Without history of documeneted CVD and LDL-C <100 mg/dL (<2.59 mmol/L) at the screening visit	LDL-C ≥70 mg/dL (1.8 mmol/L): Secondary prevention LDL-C ≥100 mg/dL (2.6 mmol/L): Primary prevention
NCT01266876	Stein (2012)	**Inclusion:** HeFH on stable statin dose (patients not on a stable statin dose (+/- ezetimibe) for 6 weeks or more, or receiving other LLT, entered a 6-week washout or statin stabilisation run-in period prior to screening) **Exclusion:** '-Patients with homozygous familial hypercholesterolaemia - type 1 or type 2 diabetes treated with insulin or poorly controlled (glycated haemoglobin ≥8·5%), - history of a recent (<6 months) cardiovascular or cerebrovascularevent or intervention.	LDL-C ≥100 mg/dL (2.6 mmol/L)

Trial name	Primary Publication	Inclusion/ Exclusion Criteria	LDL-C inclusion criteria
ODYSSEY HIGH FH	Ginsberg (2016)	**Inclusion:** Patients with HeFH on a maximally tolerated stable daily dose of statin, with or without other LLT, for at least 4 weeks (6 weeks for fenofibrate) prior to the screening visit. **Exclusion:** Known history of homozygous familial hypercholesterolemia	LDL-C ≥160 mg/dL

Table 7: Baseline Characteristics

Trial name	Primary Publication	Disease Category	Male (%)	Mean Age	Mean BMI	Mean LDL-C (mg/dL)	HeFH (%)	ASCVD (%)	CHD (%)	PAD (%)	ACS (%)	ASCVD RE (%)	Statin Intensity (%)	Eze (%)	Statin intolerant (%)
ORION-1	Ray (2017)	ASCVD	53-74%	64-63	29	125.2-131.3	5%	70-74%	NR	11-16%	NR	NR	H: 34-36% M: 34% L: 3-7%	25-26%	20-30% (assumed)
ORION-10	Ray (2020)	ASCVD	69-70%	66	32	69.6-162.7	1-1.5%	100%	90-92%	11-12%	1%	0%	H: 67-68% M: 18-20% L: 1%	10%	22%
ORION-11	Ray (2020)	ASCVD	72%	65	30	70.9-161.6	1.7%	87-88%	76-77%	9%	0-0.5%	12-13%	H: 78-79% M: 15-16% L: 0.4%	6-8%	11-12%
ODYSSEY COMBO I	Kereiakes (2015)	ASCVD	63-72%	63	32-33	100.2-106	NR	NR	78-79%	NR	NR	CHD RE: 41-48%	H: 62-65%	0% (not allowed)	NR
ODYSSEY COMBO II	Cannon (2015)	ASCVD	71-75%	61-62	30	2.7-2.8 mmol/L	NR	93-96%	88-91%	5%	NR	CHD RE: 30-32%	H: 66-67%	0% (not allowed)	NR
LAPLACE-2	Robinson (2014)	ASCVD	51-56%	60-61	NR	109	NR	NR	NR	NR	NR	NR	NR	NR (Eze treatment arm)	0%
ODYSSEY CHOICE I	Robinson (2016)	ASCVD	61-56%	61-62	30-31	112-114	7-8%	NR	NR	NR	NR	NR	NR	12-14%	NR

Trial name	Primary Publication	Disease Category	Male (%)	Mean Age	Mean BMI	Mean LDL-C (mg/dL)	HeFH (%)	ASCVD (%)	CHD (%)	PAD (%)	ACS (%)	ASCVD RE (%)	Statin Intensity (%)	Eze (%)	Statin intolerant (%)
NCT01288443	McKenney (2012)	ASCVD	32-52%	53-60	28-31	123-131	NR	7%	NR	3-10%	NR	NR	NR	0%	NR
ODYSSEY Long Term	Robinson (2015)	ASCVD	60-63%	60-61	30-31	121-122 mg/dL	17%	NR	68-70%	NR	NR	CHD RE: 41%	H: 47%	14-15%	NR
LAPLACE-TIMI 57	Giugliano (2012)	ASCVD	42-46%	60-62	29-30	3.1-3.2 mmol/L	NR	28-40%	NR	NR	14-24%	NR	H: 24-32%	9-10%	NR
FOURIER	Sabatine (2017)	ASCVD	75-76%	63	NR	Median: 92 mg/dL	NR	100%	NR	13-14%	MI: 81%, non-HS: 19%	NR	H: 69-70% M: 30-31% L: 0.3%	5%	NR
ODYSSEY EAST	Han (2020)	ASCVD	70-77%	58-59	25-26	2.8 mmol/L	0%	NR	97-98%	NR	NR	12-13%	H: 68% M: 8-10%	0% (not allowed)	NR
ODYSSEY KT	Koh (2018)	ASCVD	79%	60-61	26-27	97-99 mg/dL	NR	NR	93-99%	NR	NR	22-26%	H: 72-73%	12-14%	NR
ODYSSEY OUTCOMES	Schwartz (2018)	ASCVD	75%	59	29	92 mg/dL	NR	NR	NR	4%	100 %	NR	H: 89% M: 8-9%	3%	NR
ODYSSEY ALTERNATIVE	Moriarty (2015)	ASCVD; Statin intolerant	54-56%	63-64	28-30	187-193 mg/dL	NR	NR	43-51%	1-5%	NR	NR	NR	NR (2 week washout of Eze)	100%
ODYSSEY CHOICE II	Stroes (2016)	ASCVD; Statin intolerant	53-60%	63	29	154-163 mg/dL	8-15%	NR	47-49%	NR	NR	NR	NR	60%	NR
ODYSSEY NIPPON	Teramoto (2019)	ASCVD; Statin intolerant	62-66%	64-65	26	149-154 mg/dL	20-25%	NR	NR	0-2%	11%	NR	H: 0%	13-26%	60-75% (34% on low-dose statin)
GAUSS-2	Stroes (2014)	ASCVD; Statin intolerant	47-55%	61-62	NR	192-195 mg/dL	NR	NR	NR	NR	NR	NR		NR (Eze discontinued prior to screening)	100%

Trial name	Primary Publication	Disease Category	Male (%)	Mean Age	Mean BMI	Mean LDL-C (mg/dL)	HeFH (%)	ASCVD (%)	CHD (%)	PAD (%)	ACS (%)	ASCVD RE (%)	Statin Intensity (%)	Eze (%)	Statin intolerant (%)
GAUSS-4	Koba (2020)	ASCVD; Statin intolerant	48-52%	62-66	NR	181-192 mg/dL	NR	NR	NR	CVD or PAD: 5-25%	NR	NR	NR	NR	100%
ORION-9	Raal (2020)	HeFH	46-48%	54-55	29	151.4-154.7 mg/dL	100%	24-30%	22-29%	0-1%	NR	70-76%	H: 71-76% M: 30-40% L: 4-5%	50-56%	24-27%
RUTHERFORD-2	Raal (2015)	HeFH	54-60%	51-53	NR	3.9-4.2 mmol/L	100%	NR	NR	NR	NR	NR	NR	60%	NR
ODYSSEY FH I	Kastelein (2015)	HeFH	56-58%	52	29-30	3.7 mmol/L	100%	NR	46-48%	NR	NR	CHD RE: 15-17%	H: 83-85%	56-60%	0%
ODYSSEY FH II	Kastelein (2015)	HeFH	52-55%	53	28-29	3.4 mmol/L	100%	NR	35-38%	NR	NR	CHD RE: 5-9%	H: 87-92%	65-67%	0%
NCT01266876	Stein (2012)	HeFH	60-81%	52-56	29-31	3.6-3.9 mmol/L	100%	25-47%	NR	NR	NR	NR	NR	73%	0%
ODYSSEY HIGH FH	Ginsberg (2016)	HeFH	49-63%	50-52	29	196.3-201 mg/dL	100%	NR	43-63%	NR	NR	CHD RE: 14-18%	H: 72-74%	19-34%	NR

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; H, high-dose; HeFH, heterozygous familial hypercholesterolaemia; L, low-dose; LDL-C, low density lipoprotein cholesterol; M, medium-dose; NR, not reported

A18. Please provide the names of the statistical software used in all the analyses, including the NMA.

All Bayesian NMAs were conducted using OpenBUGS (version 3.2.3). Standard frequentist meta-analyses were conducted in R using the *metafor* package (version 2.40).

A19. **Priority** Please provide the code used for the NMA and clarify whether all the inputs needed to replicate the NMA are provided in Appendix D3. If not, please provide these also.

Analyses were performed using standard OpenBUGS code based on the NICE DSU technical support document 2 (16) for continuous (percent change in LDL-C) and binary data (safety outcomes). Where necessary, codes were adjusted for three-arm studies.

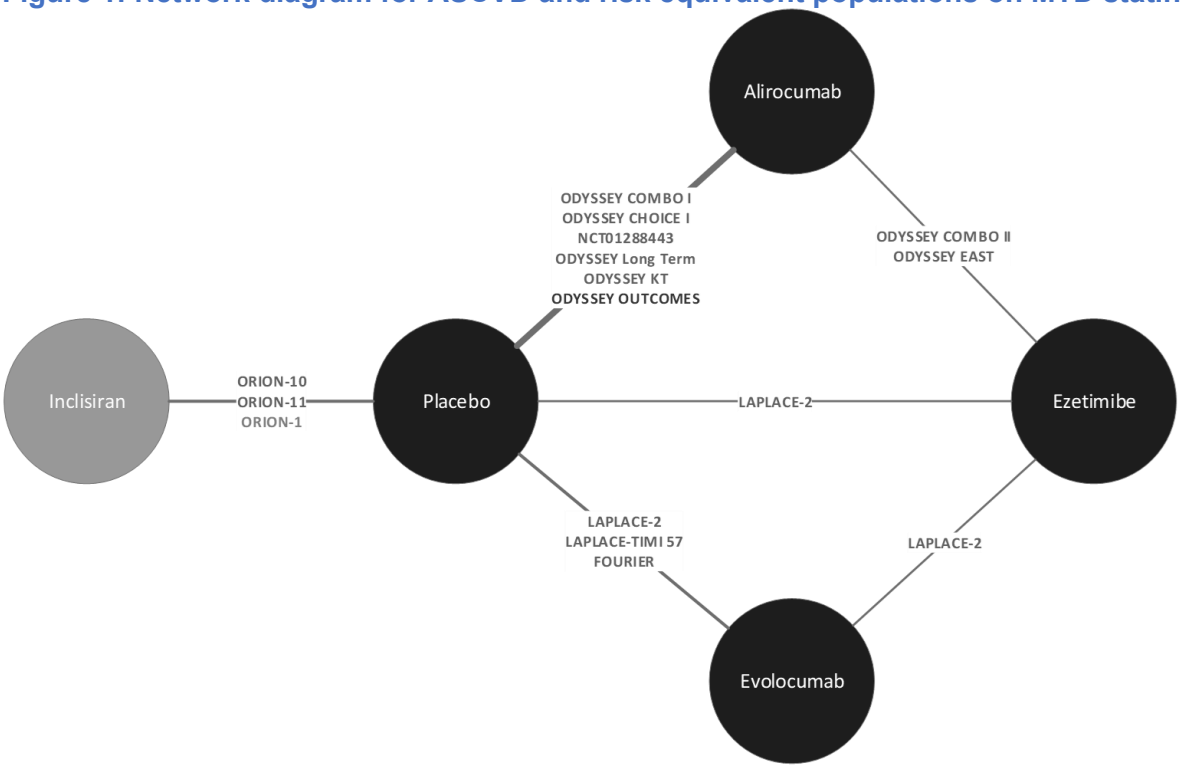
Model codes, data inputs files and initial values used to perform the analyses have been provided for ASCVD MTD percent change in LDL-C, and discontinuations due to AEs.

Data inputs presented in company submission Appendix N provide all necessary data required to replicate the analyses performed. However, during review of these tables, errors were observed in the treatment arm labelling only for several studies. Corrections have been made to these tables, and the corrected NMA technical report is included in the ERG clarification reference pack as 'ID1647 inclisiran Updated Appendix N_AIC'. Furthermore, a .csv file 'DOF (AiC) NMA Data Inputs' has been provided, which includes all data used as inputs for the analyses.

A20. Please clarify whether inconsistency or agreement between the effect estimates from direct and indirect comparison for the closed loops of the NMA were explored. Agreement between these estimates provides additional assurance that distribution of effect modifiers was comparable across the compared direct treatment comparisons.

Two closed loops were present across the analysed networks (both are in the MTD ASCVD network); one between placebo, evolocumab, and ezetimibe, and one between placebo, alirocumab, and ezetimibe (Figure 1).

Figure 1: Network diagram for ASCVD and risk equivalent populations on MTD statin



Consistency was assessed by comparing the direct relative effects (as reported by an individual study) with the indirect relative effects based on RE Bucher ITCs and those estimated based on the RE NMA for the same pair-wise contrasts, as recommended by NICE (17).

Below we provide a detailed summary of our findings for both closed loops in the ASCVD MTD network:

- **Loop #1.** The placebo/evolocumab/ezetimibe loop is created by a single multi-arm trial (LAPLACE-2), which had data on all three treatments in the loop. Mathematically, the results in the LAPLACE-2 loop must be consistent with themselves; however, given the observed heterogeneity across the three studies inconsistency could arise, if the result from LAPLACE-2 was notably different than the results for LAPLACE-TIMI or FOURIER. No evidence of inconsistency was observed; the direct estimates for ezetimibe versus placebo from LAPLACE-2 were similar with the results of the RE Bucher ITC and RE Bayesian NMA. Furthermore, the results from LAPLACE-2 for evolocumab vs placebo are between those for LAPLACE-TIMI and FOURIER.

Table 8: ASCVD MTD: Percent change LDL-C at 24 weeks – ezetimibe vs placebo for the placebo/evolucumab/ezetimibe loop

Evidence	Effect and [95%CI/CrI]
Direct estimate (LAPLACE-2)	[redacted]
Indirect (RE Bucher ITC) estimate	[redacted]
Direct + indirect estimate (RE NMA)	[redacted]

- **Loop #2.** The placebo/alirocumab/ezetimibe loop is created by independent sources of data (i.e. there were no three-armed studies contributing to this loop). Given this, the indirect evidence for the contrast of ezetimibe vs. placebo was compared to the direct evidence from LAPLACE-2. The direct and indirect estimates were again similar, suggesting no inconsistency in the network.

Table 9: ASCVD MTD: Percent change LDL-C at 24 weeks – ezetimibe vs placebo for the placebo/alirocumab/ezetimibe loop

Evidence	Effect and [95%CI/CrI]
Direct estimate (LAPLACE-2)	[redacted]
Indirect (RE Bucher ITC) estimate	[redacted]
Direct + indirect estimate (RE NMA)	[redacted]

A21. Please clarify if in the closed loops of the NMA, mixed treatment (both direct and indirect) estimates were used given there was consistency between the two.

Both direct and indirect estimates based on RE Bayesian models were used to estimate the relative effects.

Section B: Clarification on cost-effectiveness data

B1. **Priority** Page 194 of the company submission states:

"*Acute costs for CV events have been taken from NHS reference costs with post-event costs being taken from CG181 and TA393…Costs from CG181 and TA393 have been inflated from 2013/14 to 2018/19 prices using the HCHS pay and prices index (18). A systematic review of costs and resource use was carried out (Appendix I), however the sources used in previous appraisals have been retained for consistency.*"

Table 78 (page 195 company submission): Cost of CV events split by year

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

Table adapted from page 233 company submission for TA393/page 303 NICE committee papers (3)

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

B.1.1. Please confirm that the post-event costs for years 1 and 2 as showed in table above, adapted from TA393, are for cost years 2013/14 including the original page number and source from which this was extracted prior from CG181.

Section L2.3.6.3 (Page 590) of Appendices for CG181 (19) states that "*costs of health states were based on estimates of resource use that a typical adult with that CV condition would be expected to receive in line with NICE guidance and standard NHS practice. Costs were sourced from the NHS Drug Tariff, May 2014, NHS Reference costs 2012–13, PSSRU Unit Costs of Health & Social Care 2013 and BNF, May 2014. Standard dosages were taken from BNF, May 2014.*" However, no further details on the source of costs were provided.

The base year for costs in the company submission is 2020. CG181 states that the year for costs is 2014 and costs were assumed to be for the years 2013/14 when applying inflation factors. Inflation factors from the HCHS pay and prices index were applied for the years 2014/15 and 2015/16 (0.90% and 1.30% increase on the

previous year, respectively). This index was discontinued in 2016 and for the years 2016/17, 2017/18 and 2018/19 the NHSCII pay and prices index has been applied (2.12%, 1.16% and 2.31% increase on the previous year, respectively). This gives a total increase in costs of 8.03%.

B.1.2. You have stated post-event costs are used in this CS to 'retain consistency from previous appraisals', however, an alternative method of costing acute CV events has been used. These have generated notably different estimates as seen when comparing figures in the above two tables. Please provide further rationale for your choice of costing acute CV events.

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 (which are from 2014), as this will better reflect any changes in the provision of care.

Table 10 presents the event costs had we updated all costs from TA393. Table 11, Table 12 and Table 13 present the cost-effectiveness results of scenario analyses assuming the costs in Table 10 for the secondary prevention ASCVD, PPER and primary prevention HeFH populations, respectively. The impact of these changes on results is minimal and ICERs for inclisiran are reduced slightly in all cases.

Table 10: Event costs updated from TA393

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.

Table 11: Results for the ASCVD population assuming the event costs in Table 10

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 12: Results for the PPER population assuming the event costs in Table 10

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 13: Results for the primary prevention HeFH population assuming the event costs in Table 10

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

B2. **Priority** Please clarify if time to discontinuation information is available for people randomised to inclisiran. Additionally, what assumptions are being made following discontinuation of inclisiran. For example, what treatment do people receive?

Tables 14.1.7.1 of the CSRs for ORION-9, -10 and -11 present the disposition of patients at each visit in the trials, including the number of discontinued patients. These data are summarised in Table 14. When a patient discontinues inclisiran, it is assumed that their background therapies remain unchanged, thus they would continue on SoC (statins +/- ezetimibe).

Table 14: Number of discontinued patients in the inclisiran arm by study visit in ORION-9, -10 and -11

Visit	ORION-9 n (%)	ORION-10 n (%)	ORION-11 n (%)
Day 1	[redacted]	[redacted]	[redacted]
Day 30	[redacted]	[redacted]	[redacted]
Day 90	[redacted]	[redacted]	[redacted]
Day 150	[redacted]	[redacted]	[redacted]
Day 270	[redacted]	[redacted]	[redacted]
Day 330	[redacted]	[redacted]	[redacted]
Day 450	[redacted]	[redacted]	[redacted]
Day 510	[redacted]	[redacted]	[redacted]
Day 540	[redacted]	[redacted]	[redacted]

B3. **Priority** Pages 173-174, company submission state that as per TA393, a mixed cohort of patients was modelled including patients with a history of myocardial infarction, unstable angina, other coronary heart diseases, ischaemic stroke, and peripheral artery disease and this was captured by running the model for each cohort and the results are averaged over the sub-populations. Please clarify what methods were used to address mixed cohort of patients when undertaking the probabilistic sensitivity analysis.

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:

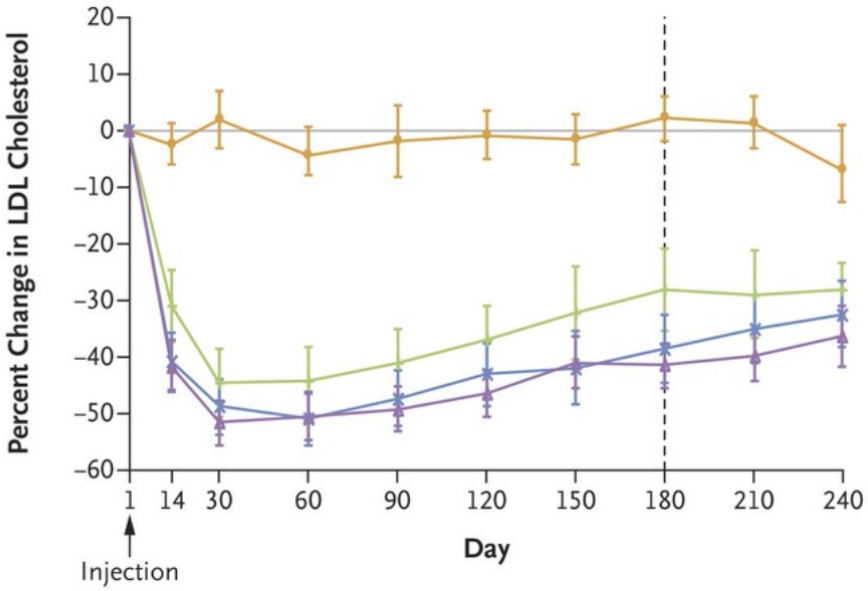
1. Set the population to model population 1 (Primary prevention HeFH)
2. Run the PSA and copy costs and QALYs for each comparator from each simulation
3. Repeat for populations 2 to 8 (Secondary prevention HeFH to PPER)
4. Calculate the weighted average costs and QALYs for each arm for each simulation, 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.

B4. **Priority** On page 197 company submission the company made some assumptions for when people discontinue therapy their LDL-C returns to baseline in the following cycle. The company stated that 'other therapies are dosed more frequently than inclisiran and LDL-C levels are expected to return to baseline at a faster rate.' Please clarify what rate(s) are being used for people who discontinue other therapies.

While it is anticipated that in clinical practice patients discontinuing other therapies would return to baseline levels of LDL-C at faster rates than those discontinuing inclisiran, for the purposes of the model it is assumed that all patients would return to baseline at the same rate. This is considered to be a conservative assumption for inclisiran as it ignores the residual benefit that may be observed following a patient's final dose of inclisiran.

This was observed during the Phase 2 study ORION-1, in which a single-dose regimen was also considered (20); LDL-C levels were still significantly below baseline levels 240 days following injection (Figure 2).

Figure 2: Changes in LDL-C levels with the single dose regimen



No. at Risk										
Single-dose placebo	65	65	65	62	64	65	62	64	62	27
Single-dose inclisiran, 200 mg	60	60	59	60	60	58	60	60	60	49
Single-dose inclisiran, 300 mg	61	61	61	61	60	61	60	60	61	50
Single-dose inclisiran, 500 mg	65	65	65	62	64	60	63	60	61	57

Source: Ray, 2017 (20).

B5. Please clarify if there is a scenario presented using transitions based on the Clinical Practice Research Datalink (CRPD) information.

For the base-case analyses in the secondary and primary prevention populations, data from the CPRD analysis were used to inform all transitions. The only exception to this is the subgroup analysis for secondary-prevention HeFH patients, where the Mohrschladt data (21) were used for the base-case analysis. A scenario presenting the results for this population using data from the CPRD analysis was also presented in Table 110 of the company submission.

B6. The company stated that previous meta-analyses on the effect of lowering LDL-C on event rates have reported a log-linear relationship. Please clarify if other relationships have been considered in scenario analysis.

We have only considered log-linear relationships, as per TA393 (3) and TA394 (4). The use of a linear relationship would imply a greater number of events avoided, and therefore the log-linear relationship was considered conservative. Additionally a linear relationship of the form below would not produce consistent results, as explained below.

$$E_1 = E_0 * (1 - (1 - \alpha)(L_0 - L_1))$$

Using the log-linear relationship, if a patient experienced an increase in LDL-C, followed by a decrease of the same absolute amount, their risk after this would be the same as their baseline risk. If E_0 is the baseline risk, L_0 the baseline LDL-C, L_1 the increased LDL-C, E_1 the risk after the increase in LDL-C and E_2 the LDL-C after returning to baseline then using a log-linear relationship:

$$E_1 = E_0 * \alpha_i^{L_0 - L_1}$$

$$E_2 = E_1 * \alpha_i^{L_1 - L_0} = E_0 * \alpha_i^{L_1 - L_0} \alpha_i^{L_0 - L_1} = E_0 * \alpha_i^{L_1 - L_0 + L_0 - L_1} = E_0$$

This means that after increasing then decreasing LDL-C by the same absolute amount, the risks remain the same. Applying the linear relationship:

$$E_1 = E_0 * (1 - (1 - \alpha)(L_0 - L_1))$$

$$\begin{aligned} E_2 = E_1 * \big(1 - (1 - \alpha)(L_1 - L_0)\big) \\ = E_0 * \big(1 - (1 - \alpha)(L_0 - L_1)\big) * \big(1 - (1 - \alpha)(L_1 - L_0)\big) \\ = E_0 * (1 - ((1 - \alpha)(L_0 - L_1))^2) \end{aligned}$$

As $((1 - \alpha)(L_0 - L_1))^2$ will be greater than zero, this implies that $E_2 < E_0$, i.e. the risk after adjustment will be lower than the risk at baseline, which would not be consistent.

Since the model adjusts baseline risks to account for differences in LDL-C between the modelled population and the population in which risks were assessed to obtain risks for the SoC arm, then adjusts these again to account for the effect of treatment, a linear relationship is not judged to be appropriate.

B7. **Priority** Please report the confidence intervals for the rate ratio (RR) per 1.0 mmol/L reduction in LDL-C (Year 2+) used in scenario analysis. (Presented in table 70, page 187 of company submission) Also, what RR is used for Stroke (any) in the scenario analysis?

Rate ratios in the scenario have been calculated by adjusting the base-case values by a factor calculated from Collins et al, 2016 (22), and do not have associated confidence intervals.

The estimation of confidence intervals for the ratio of two values is a non-trivial problem. Methods such as Fieller's theorem have been proposed, however such estimations rely on quantities which would require access to the original data used by Collins et al; for example information on the correlation between parameters. An alternative approach would be to produce bootstrapped estimates of the confidence interval, but again this would require access to the underlying data.

To estimate confidence intervals, an estimate has been made assuming no correlation between the means used to calculate the ratio. This assumption is expected to generate a conservative estimate of the uncertainty around the confidence interval. Standard errors have first been estimated according to the following formula:

$$a = \frac{b}{c} \; or \; a = b * c, \qquad \frac{se_a}{a} = \sqrt{\frac{{se_b}^2}{b} + \frac{{se_c}^2}{c}}$$

Where confidence intervals for rate ratios were reported without standard errors, standard errors for each point estimate were calculated from confidence intervals assuming a normal distribution. Results are presented in Table 15

Table 15: Estimated confidence intervals in the scenario analysis

	Mean	SE	LCI	UCI
Revascularisation	0.71	0.02	0.67	0.75
UA	0.69	0.02	0.65	0.73
MI	0.69	0.02	0.65	0.73
IS	0.75	0.04	0.67	0.83
CV death	0.80	0.03	0.75	0.85

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

A rate ratio for Stroke (any) is not applied in the model, as only ischaemic strokes are considered in the analysis in line with TA393.

B8. Page 175 company submission, states *that '…and thus in line with previous submissions, the following relationship is applied*:' Please provide the references for these previous submissions.

In TA393 (Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia), the company submission (Page 207) provides the following relationship:

$$\frac{E_{0i}-E_i}{E_{0i}} = 1 - \alpha_i^{(L_0 - L_i)} \quad (1)$$

$$E_i = E_{0i}[\alpha_i^{(L_0 - L_i)}] \quad (2)$$

$$\ln(E_i) = \ln(E_{0i}) + (L_0 - L_i)\ln(\alpha_i) \quad (3)$$

Where:

- L_0 is the baseline LDL-C level in mmol/L
- L_i is the new LDL-C level in mmol/L
- E_{0i} is the one-year probability for experiencing event i at the baseline LDL-C level of L_0
- E_i is the one-year probability for experiencing event i at the LDL-C level of L_i
- α_i is the "rate ratio" (RR) per unit change in LDL-C for event i

In TA394 (Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia), the company submission (Page 197) states:

- *"For every mmol/L lowering of LDL-C (dLDL-C), the rate ratio of CV events is given by the corresponding event specific rate ratio in Table 5-12 to the power of dLDL-C"*

B9. In the systematic review of cost-effectiveness studies, full references are only available for the UK studies and the newer Australian study by Kam, et al.(2020). Please provide a list of full references for included studies as only first author surname and year are given. Please also provide a list of excluded studies (161 according to flow diagram) and reasons for their exclusion, as these are not supplied.

The list of full references for included (N=71 publications and 15 HTAs) and excluded studies (N=161, as per PRISMA flow chart) along with the reasons for exclusion are provided in Table 16 and Table 17, respectively in Appendix 1.

After the cost-effectiveness SLR was conducted, a single economic evaluation was identified through desk research (23). However, this paper takes the perspective of the Australian healthcare payer and does not cover all relevant populations.

B10. In the systematic review of health-related quality of life (HRQoL) studies, please provide a list of full references for the 214 included studies. Please also provide a list of excluded studies (384 + 184 according to the two flow diagrams) and reasons for their exclusion, as these are not supplied.

The list of full references for included (N=214) and excluded studies (N=384+185, according to two PRISMA flow charts) along with the reasons for exclusion are provided in Table 18 and Table 19, respectively in Appendix 2.

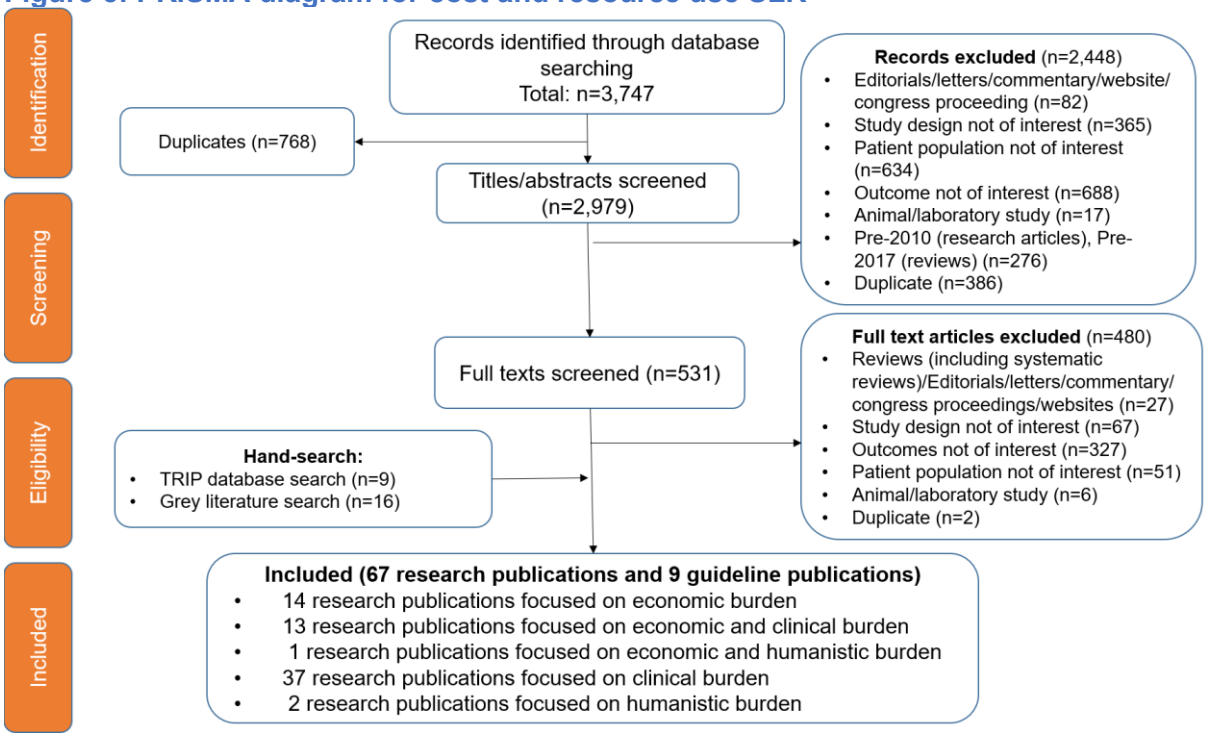
Please note that in the update SLR there were 185 exclusions, rather than 184 as mentioned in Question B10.

Section C: Textual clarification and additional points

C1. In the systematic review of costs and resource use 28 studies were included and full references are provided for these. Please provide a list of excluded studies with reasons, and numbers included/excluded at each stage. Ideally, this would be in the form of a PRISMA flow diagram.

A PRISMA flow diagram with details on number of included and excluded studies at each screening stage is provided in Figure 3.

Figure 3: PRISMA diagram for cost and resource use SLR



The list of full references for included (N=76) studies are provided in Table 20 and Table 21 in Appendix 3. A list of excluded studies (N=480), along with the reasons for exclusion is provided in Table 22 in Appendix 3.

Please note that this SLR also identified studies for clinical and humanistic burden, and therefore the reference list for these studies is also provided along with the economic burden (cost and resource use) included studies list.

C2. Figure 29: (page 116): Please clarify if this is the population on maximally tolerated dose (MTD) statin. Please indicate in the title of the diagram.

Yes, this refers to MTD statin. The title should be: 'Network diagram for HeFH population on MTD statin'.

C3. Page 168, company submission states '… *and clinical experts in the UK have recommended 2.6mmol threshold (Section).* Please clarify which section is being cross-referenced.

The cross-reference should link to Section B.1.3.5.

C4. There are two cited unpublished '=' references in CS Document B that cannot be identified in the 'data on file' or 'reference pack' folders supplied:

8. Data on file [INC-DOF-002]. IQVIA analysis of HES (NHS Digital. Hospital Episode Statistics) Data. *Cited on pages 13, 32, and 34 of CS Doc B*

60. Data on file [INC-DOF-002]. LPD, IQVIA Solutions UK Ltd, incorporating data derived from THIN, A Cegedim Database, June 2020. Cited on page 42 of CS Doc B

Please provide these documents.

Please see the reference pack for the document 'DOF [CiC] Inclisiran – Patient Journey Analysis using Real World Data'. The two references were derived from one document generated by IQVIA and previously shared in the company submission reference pack as 'Data on file [INC-DOF-002]'. This document contains the two data sources i.e. the IQVIA analysis of HES and the IQVIA analysis of THIN derived data. Please note that since submitting the NICE submission, IQVIA has updated the document and therefore we have provided the updated version from October 2020 (one slide [slide 38] was added in the new version). We have also highlighted which slides each reference relates to:

8. Data on file [INC-DOF-002]. IQVIA analysis of HES (NHS Digital. Hospital Episode Statistics) Data, October 2020. Cited on pages 13 (slide 37), 32 (slide 37 & 38), and 34 (slide 35) of the company submission

60. Data on file [INC-DOF-002]. LPD, IQVIA Solutions UK Ltd, incorporating data derived from THIN, A Cegedim Database, October 2020. Cited on page 42 (slide 87) of the company submission.

C5. A file in the 'data on file' folder has been provided which has not been cited in the company submission that we can't see (Filename: Data on file [INC-DOF-0010]. PPER prevalence estimation. Please clarify what this is for and where it can be located in the submission.

Please note that this reference is cited in the Budget Impact Analysis.

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Appendices

Appendix 1: Cost-effectiveness SLR references

Complete reference list for included studies – cost-effectiveness SLR

Table 16: References included in the SLR – cost-effectiveness SLR

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Appendix 2: HRQoL SLR references

Complete reference list for included studies – HRQoL SLR

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Table 19: Excluded records by reason – HRQoL SLR

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Appendix 3: Cost and resource use SLR references

Complete reference list for included studies – Cost and resource use SLR

Table 20: References included in the SLR – cost and resource use SLR

Outcome	Reference associated
Economic burden	Bahia, L. R.; Rosa R. S.; Santos R. D.; Araujo D. V. Estimated costs of hospitalization due to coronary artery disease attributable to familial hypercholesterolemia in the Brazilian public health system. 2018. Archives of Endocrinology and Metabolism. 62 (3): 303–308. Khera, R.; Valero-Elizondo J.; Okunrintemi V.; Saxena A.; Das S. R.; de Lemos J. A.; Krumholz H. M.; Nasir K. Association of out-of-pocket annual health expenditures with financial hardship in low-income adults with atherosclerotic cardiovascular disease in the United States. 2018. JAMA Cardiology. 3 (8): 729–738. Mundal, L.; Veierod M. B.; Halvorsen T.; Holven K. B.; Ose L.; Iversen P. O.; Tell G. S.; Leren T. P.; et al. Cardiovascular disease in patients with genotyped familial hypercholesterolemia in Norway during 1994–2009, a registry study. 2016. European Journal of Preventive Cardiology. 23 (18): 1962–1969. Power, T. P.; Ke X.; Zhao Z.; Bonine N. G.; Cziraky M. J.; Grabner M.; Barron J. J.; Quimbo R.; et al. Clinical characteristics, patterns of lipid-lowering medication use, and health care resource utilization and costs among patients with atherosclerotic cardiovascular disease. 2018. Vascular Health and Risk Management. 14: 23–36. Salami, J. A.; Valero-Elizondo J.; Ogunmoroti O.; Spatz E. S.; Rana J. S.; Virani S. S.; Blankstein R.; Younus A.; et al. Association between modifiable risk factors and pharmaceutical expenditures among adults with atherosclerotic cardiovascular disease in the United States: 2012–2013 Medical Expenditures Panel survey. 2017. Journal of the American Heart Association. 6 (6): e004996. Shen, X.; DiMario S.; Philip K. Gender disparities in health resource utilization in patients with atherosclerotic cardiovascular disease: a retrospective cross-sectional study. 2019. Advances in Therapy. 36 (12): 3424–3434. Weng, W.; Kong S. X.; Ganguly R.; Hersloev M.; Brett J.; Hobbs T.; Baeres F. M. M. The prevalence of cardiovascular disease by vascular bed and impact on healthcare costs in a large, real-world population with type 2 diabetes. 2020. Endocrinology Diabetes & Metabolism. 3 (2): e00106. Zhao, Z.; Zhu Y.; Fang Y.; Ye W.; McCollam P. Healthcare resource utilization and costs in working-age patients with high-risk atherosclerotic cardiovascular disease: findings from a multi-employer claims database. 2015. Journal of Medical Economics. 18 (9): 655–665.
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Table 21: References included in the SLR identified through hand searching/grey literature search – Cost and resource use SLR

Outcome	Reference associated
Economic burden	Banefelt, J.; Hallberg S.; Fox K. M.; Mesterton J.; Paoli C. J.; Johansson G.; Levin L. A.; Sobocki P.; et al. Work productivity loss and indirect costs associated with new cardiovascular events in high-risk patients with hyperlipidemia: estimates from population-based register data in Sweden. 2016. European Journal of Health Economics. 17 (9): 1117–1124. Chapman, R. H.; Liu L. Z.; Girase P. G.; Straka R. J. Determining initial and follow-up costs of cardiovascular events in a US managed care population. 2011. BMC Cardiovascular Disorders. 11: 11. Hallberg, S.; Gandra S. R.; Fox K. M.; Mesterton J.; Banefelt J.; Johansson G.; Levin L. A.; Sobocki P. Healthcare costs associated with cardiovascular events in patients with hyperlipidemia or prior cardiovascular events: estimates from Swedish population-based register data. 2016. European Journal of Health Economics. 17 (5): 591–601. Henk, H. J.; Paoli C. J.; Gandra S. R. A retrospective study to examine healthcare costs related to cardiovascular events in individuals with hyperlipidemia. 2015. Advances in Therapy. 32 (11): 1104–1116. Lucioni, C.; Mazzi S.; Rossi E.; Rielli R.; Calabria S.; Maggioni A. P.; Roni R.; De Marco A.; et al. Therapeutic strategies and health costs of patients admitted for a cardiovascular event in Italy. 2016. Global & Regional Health Technology Assessment. 3 (2): 80–91. Zhang, D.; Cogswell M. E.; Wang G.; Bowman B. A. Evidence of dietary improvement and preventable costs of cardiovascular disease. 2017. American Journal of Cardiology. 120 (9): 1681–1688.
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Clinical burden *(not of interest for Appendix)*	Wang, X.; Cai G.; Wang Y.; Liu R.; Xi Z.; Li G.; Wen W.; Wu Y.; et al. Comparison of long-term outcomes of young patients after a coronary event associated with familial hypercholesterolemia. 2019. Lipids in Health and Disease. 18 (1): 131.
Humanistic burden *(not of interest for Appendix)*	Mata, N.; Alonso R.; Banegas J. R.; Zambon D.; Brea A.; Mata P. Quality of life in a cohort of familial hypercholesterolemia patients from the south of Europe. 2014. European Journal of Public Health. 24 (2): 221–225.
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Complete reference list for excluded studies – cost and resource use SLR

Table 22: Excluded records by reason – cost and resource use SLR

Ineligible patient population
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Additional Clarification questions

December 2020

File name	Version	Contains confidential information	Date
Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]	1	Yes	15 December 2020

Section B: Clarification on cost-effectiveness data

B1. Additional clarification: Could the company provide the latest version/ new model used to calculate the ICERs you provided in response to clarification question A14 (presented in tables 3 and 4)?

Please find a version of the model which includes ezetimibe as an active comparator in the accompanying file of the response.

B2. Additional clarification: In the decision problem (Table 1 of CS) you have stated:

"The population described in the final scope broadly captures the anticipated licensed indication for inclisiran.
However, [redacted]

[redacted]

Could the company confirm that reimbursement is sought for the whole population for which market authorisation is (likely to be) approved or does your agreement stipulate reimbursement for only those in the [redacted]?

The population for which reimbursement is sought in this submission is as per Table 1 of the CS:

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 (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.

[redacted]

Section C: Textual clarification and additional points

C1. **Additional clarification:** For the ORION studies, we are unable to find the data on patients that are intolerant to statins. CSRs of ORION 10 and 11 refer to Tables 14.1.11.1.1 that are not provided. We are after the number of patients and if possible baseline characteristics stratified for intolerant to statins patients from ORION studies. Can the company kindly provide these tables for ORION 9,10 and 11?

Tables providing patient baseline characteristics for patients intolerant to statins from ORION 9, 10 and 11 are provided in the accompanying file of the response.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Thank you for agreeing to give us your organisation's views on inclisiran and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	HEART UK- The Cholesterol Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	HEART UK is the Nation's Cholesterol Charity providing support to individuals with raised cholesterol, atherosclerosis and other lipid conditions. We provide high quality literature, a Cholesterol Helpline run by cardiac nurses and dietitians, an extensive website, a range of educational videos, the Ultimate Cholesterol Lowering Plan© and a range of electronic communication tools aimed at increasing the awareness of cholesterol. HEART UK also supports the health care professionals who work and care for patients (and their families) with raised and unhealthy patterns of high cholesterol and other dyslipidaemias. HEART UK hosts a world class annual scientific conference and other networking events for clinicians, researchers, GP's, nurses and dietitians. The charity maintains a health professional membership scheme, provides resources and training to health care professionals.
4b. Has the organisation received any funding from the manufacturer(s) of inclisiran and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Novartis have supported an audit of lipid clinics to survey understanding of the testing of LPa, sponsorship of our annual conference, CVD Collaborative membership and primary care education programme.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have a Cholesterol Helpline with direct contact via telephone and email. The helpline supports people with information to make informed choices. Additionally, we have an extensive website that receives over 4million views a year and engagement on social media. Our e-newsletter has over 35,000 subscribers.
Living with primary hypercholesterolaemia or mixed dyslipidaemia	
6. What is it like to live with primary hypercholesterolaemia or mixed dyslipidaemia? What do carers experience when caring for someone with the condition?	NHS Health Checks, which includes a cholesterol test, are important cornerstone of CVD prevention and can be the first indication of a need for treatment. However, NHS Health Checks are delivered inconsistently across the country with very poor uptake in many places. Diet and lifestyle advice and medication to treat high cholesterol following an NHS Health Check, where a patient has raised LDL-C also varies enormously across the country. In 2020 97% of NHS Health Checks were cancelled. Access to cholesterol testing is variable and we regularly hear reports of people being denied access to a test, including people where a family history indicates familial hypercholesterolaemia.

	Most people with hypercholesterolaemia show no symptoms. In some people with familial hypercholesterolaemia (FH), it can cause xanthomas (fatty deposits often on the knuckles and ankles), raised, pale, yellowish patches around the eyes and on the eyelids (xanthelasma and arcus corneae (cholesterol deposits in the eyes). Often patients are reluctant to express doubts and concerns about medicines and frequently will stop taking medicine without exploring all additional alternatives. For example, 75% of people started on a statin discontinuing treatment within 2 years and will be at an increased risk of major CV events. Those at high CVD risk who report a potential intolerance to recommended high intensity statin treatment may be offered a lower dose statin, an alternative statin or be advised to stop taking statins for 4 – 6 weeks before ezetimibe. This pathway may not always be completed by many patients because it is time consuming and doesn't demonstrate any positive benefit for the patient and will account for some of the variations in prescribing and patients discontinuing treatment. currently PCSK9 inhibitors are under used by 60-70% and they depend on meeting a strict criteria – having FH or heart disease and an LDL level ranging from 3.5 – 5 depending on their condition. We know many people, particularly younger men with underling heart disease who have issues taking statins but miss out on PCSK9 because their LDL is too low (even if by 0.5 of a mmol/L. Some have been told they could have access to PCSK9i if they had worsening of their disease or had a heart attack (or have another heart attack). A recent caller to our helpline said that he was intolerant to statins and had tried four different types. He said it felt as though his muscles were on fire and he had stopped all treatment adding "I feel like I am on death row waiting for my time up." We have heard that some older people i.e. over 75 have been told they are "too old" to receive statins or that there is no point in trying a statin as it won't work for them. Women are also sometimes not thought to be a high risk for heart disease even though they may have high cholesterol/other risk factors (as shown in JBS3 example)- particularly younger women, we have also come across younger people (men and women) with very high levels of cholesterol not being identified as being at risk because of their lower age (with the concept atherosclerotic heart disease only occurs in older people).

Current treatment of primary hypercholesterolaemia or mixed dyslipidaemia in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	
8. Is there an unmet need for patients with primary hypercholesterolaemia or mixed dyslipidaemia?	Over half the adult population in England need to take action to manage their cholesterol. For many people, lifestyle changes on their own are not enough to bring their high cholesterol down to a healthier level to lower the risk of heart disease. The current lipid lowering therapies are very effective but adherence is very poor and patients are left exposed to the risk of CVD.
Advantages of inclisiran	
9. What do patients or carers think are the advantages of inclisiran?	A twice yearly treatment would be workable in a GP setting – as a GP is more accessible than hospital appointment, however depending on condition the reason for referral to secondary care ie lipid clinic is to have inherited conditions investigated, genetic testing and family cascade screening commenced which currently is not happening in GP surgeries. Comments and queries we get on our helpline are from people getting side effects from statins and saying their GPs don't know what to do next i.e take a statin holiday, restart a lower dose statin or switch to another group, try a hydrophilic statin over a lipophilic statin ie try rosuvastatin instead of atorvastatin, try ezetimibe etc. The adherence to lipid lowering medication would improved since inclisiran is only twice yearly and the longer term benefits to overall CVD will be much greater than the treatments currently available.

Disadvantages of inclisiran	
10. What do patients or carers think are the disadvantages of inclisiran?	
Patient population	
11. Are there any groups of patients who might benefit more or less from inclisiran than others? If so, please describe them and explain why.	Cardiovascular disease (CVD) is the underlying cause of 26% of all deaths in the UK, which includes heart attacks, strokes and dementia. This equates to approximately 160,000 deaths each year or an average of 435 people each day. At least, 42,000 of these deaths occur prematurely and, in many cases, can be prevented. Over half the adult population in England have raised cholesterol yet accessing cholesterol test to measure cholesterol levels is a serious barrier and adherence to medication, usually statins is very poor and reportedly 75% of patients stop taking lipid lowering therapies after years.
Equality	
12. Are there any potential equality issues that should be taken into account when considering primary hypercholesterolaemia or	1. Those living in England's most deprived areas are almost 4 times as likely to die prematurely from CVD than those in the least deprived areas. 2. Having a poor diet and being overweight or obese increases the risk of developing CVD. Between 1993 and 2000, there was a sharp increase in obesity, though the rate of increase has since slowed. According to NHS Digital's Health Survey for England, in 2019 36% of adults were overweight and 28% were obese. People living in the most deprived areas had the highest prevalence of obesity and very high waist circumference.

mixed dyslipidaemia and inclisiran?	3. Compared with the general population, people with severe mental illness are much more likely to develop and die from preventable physical health conditions, like CVD. This increased risk is largely caused by modifiable lifestyle factors, many of which people with severe mental illness may find more difficult manage than the general population. 4. People with learning disabilities are at increased risk of developing CVD from both genetic factors and lifestyle factors such as poor diet and inactivity.
Other issues	
13. Are there any other issues that you would like the committee to consider?	There are already too many barriers to prevent patients from accessing effective treatments that they are willing to take for the rest of their lives, starting from a point of poor awareness of the importance of managing healthy cholesterol, getting a test, taking action and onwards to treatment options. Inclisiran offers a solution to the long term treatment of patients, which will lead to a reduction in the number of heart attacks, strokes and other consequences of poorly managed and high cholesterol by introducing an additional option that can be more accessible with better adherence.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Long term adherence to lipid lowering therapies is very poor • Access to long term treatment remains very poor • CVD is worsening • There are already too many barriers to effective treatments that are accepted by the patient. No more should be introduced.	

- Statin intolerance is a concern to patients
-
-
-

Thank you for your time.

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

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None

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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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

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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]

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 ***[redacted]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 (***[redacted]16 to ***[redacted]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 ***[redacted]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

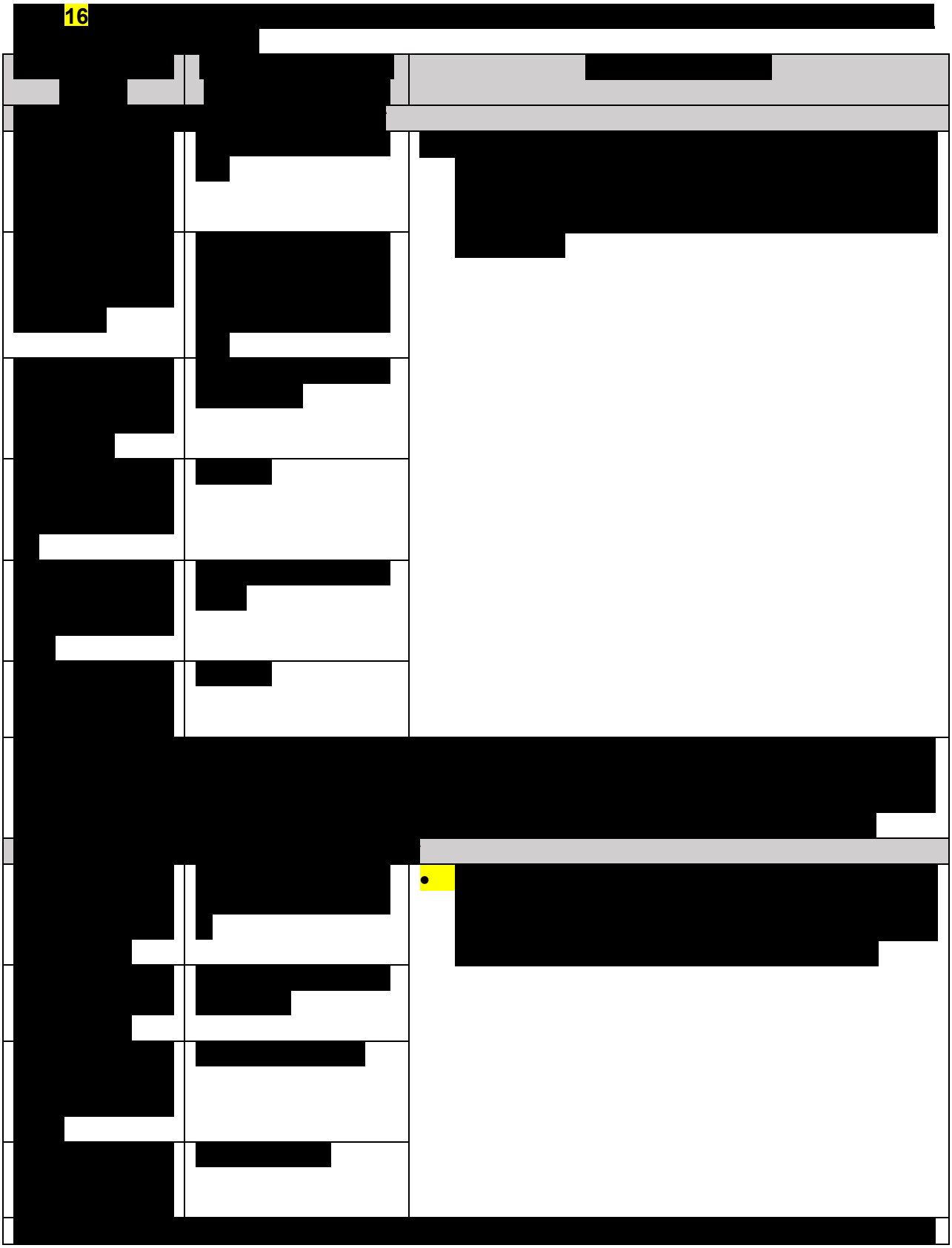
Effect modifiers	The company's and ERG comments
Population characteristics	
Background Ezetimibe	**The company's assumptions and recommendations:** Perform analyses without consideration of background ezetimibe as an effect modifier. Subgroup data for % change in LDL-C presented by two of the included 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	

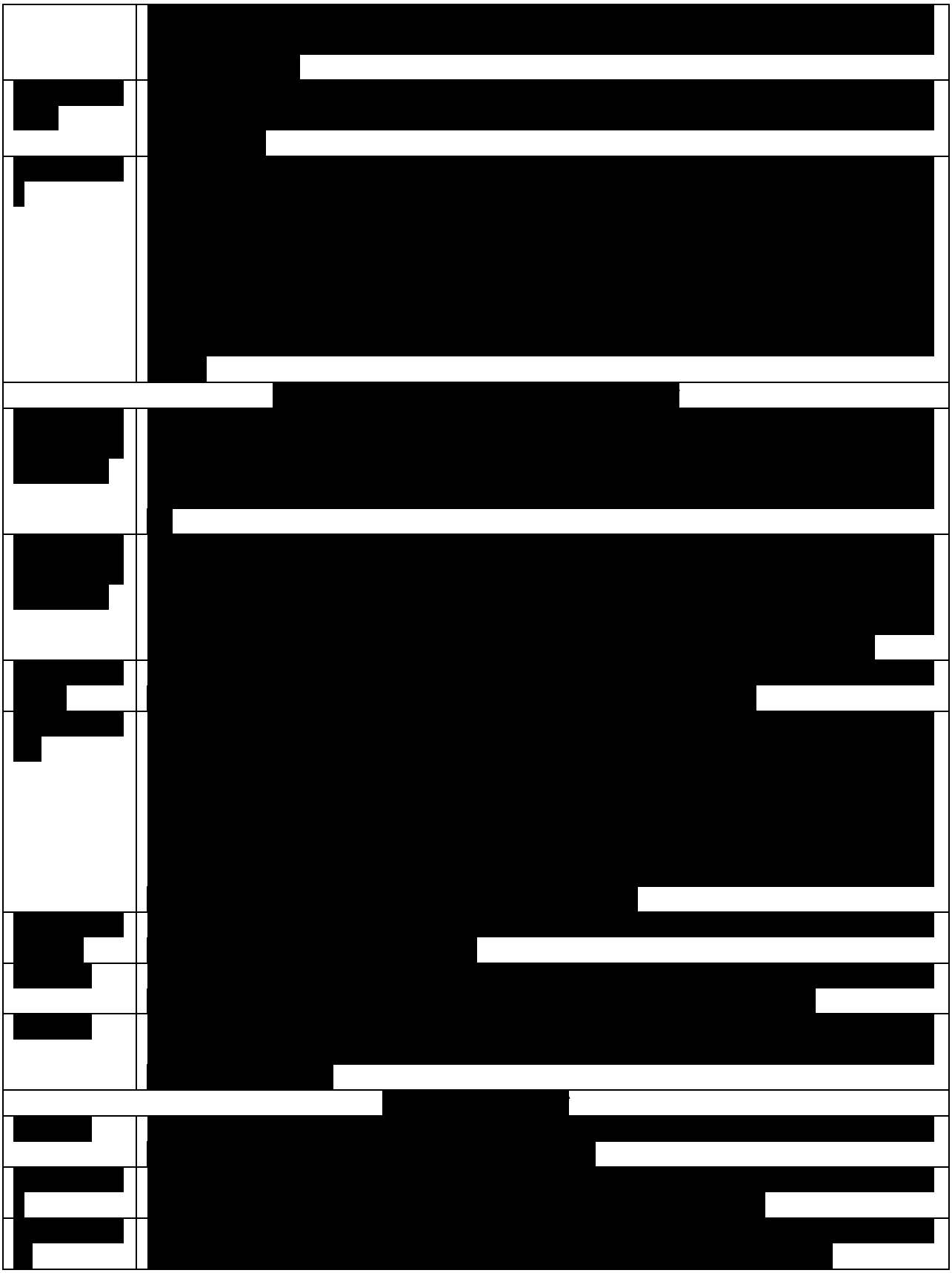


* Studies underlined used Alirocumab 150mg Q2W

[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

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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 (%)

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 (%)	ASCVDRE (%)	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

[redacted]

- 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]

  ASCVD and ASCVD PPER intolerant to statins group

- [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.

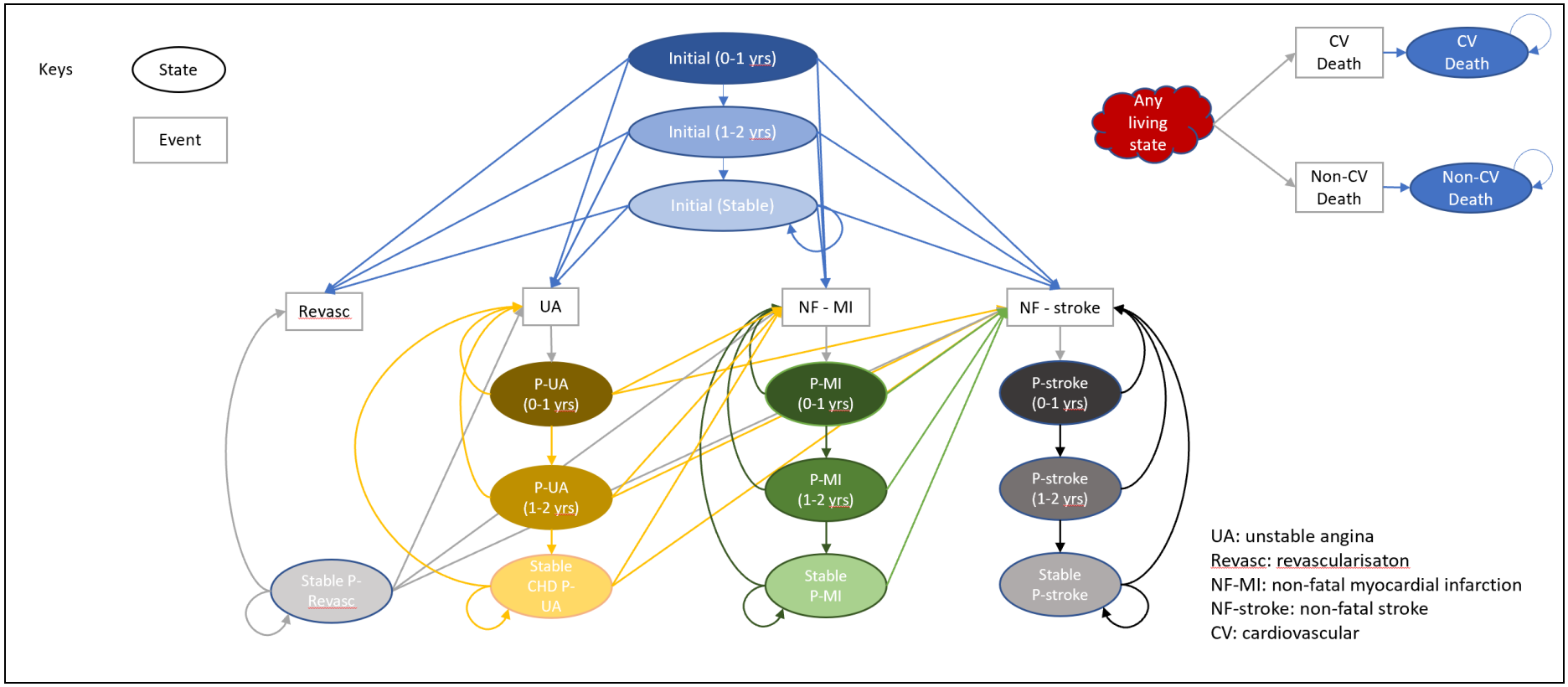

Figure 1. Illustrative Markov model structure

The model comprises 15 mutually exclusive discrete health states (see **Error! Reference source not found.**) 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 **Error! Reference source not found.** 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] (**Error! Reference source not found.**) 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**Error! Reference source not found.**
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 are on maximally tolerated statins, which is not the case for the CPRD analysis, and by using PLD in the model we	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 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]

[redacted]

[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]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[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 (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**), then cost-effectiveness acceptability curves (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**) 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. **Error! Reference source not found.** shows that there was little uncertainty around the total costs and total QALYs for across all treatment strategies.

[redacted]

(**Error! Reference source not found.**).

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]

[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. **Error! Reference source not found.** and **Error! Reference source not found.** 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)
[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]
ICER, incremental cost-effectiveness ratio; PPER, primary prevention with elevated risk; QALY, quality adjusted life year; SoC, standard of care						

[redacted]

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. **Error! Reference source not found.** and **Error! Reference source not found.** 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,

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

Error! Reference source not found. to **Error! Reference source not found.** 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 **Error! Reference source not found.** and **Error! Reference source not found.**, these results showed that the model was sensitive [redacted]. However, in the HeFH population (**Error! Reference source not found.**), 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 **Error! Reference source not found.** 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]	[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 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]	[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 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]	
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.

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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	<table><tr><th>Intervention</th><th>Comparator</th><th>ICER Cost/ QALY</th></tr><tr><td>Inclisiran + statin (+/- Ezitimibe)</td><td>Statin (+/- Ezitimibe)</td><td>$125,732</td></tr></table>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]

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 28 January 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Factually inaccurate statements

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pages 8, 21, 124 and 139 of the ERG report state: [redacted] *and does not address the full scope of the decision problem*."	Please amend this wording as follows: [redacted] *and does not address the full scope of the decision problem.*"	The current statement is factually inaccurate. The [redacted] threshold is not narrower than the population for which we are seeking reimbursement. The ERG report even explains in the paragraph above that the *"The company have sought to align the population in the submission with that in* [redacted]	We have removed the words [redacted] from the pages requested.
Pages 8 and 20 of the ERG report state: "*The ERG noted that a lack of genetic testing for all suspected cases may result in cases either being missed or being classified into other population groups (E.g. PPER or ASCVD)*."	Please amend this wording as follows: "*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 current statement is misleading and as such, factually inaccurate.	We have added ***FH*** to improve clarity of the statement on both pages.
Pages 8, 11, 20, 21, 25, 123, 138, 190 of the ERG report use the phrase: *"… anticipated marketing authorisation…"*	Please amend this wording as follows: "…~~***anticipated***~~ *marketing authorisation*…"	The marketing authorisation was received in December 2020.	We have removed the word ***anticipated*** from all pages as requested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 2 on page 26 the report state: [redacted]	Please amend this wording as follows: [redacted]	The current statement is factually inaccurate. The [redacted] threshold is not narrower than the population for which we are seeking reimbursement. The population modelled is aligned with that in which reimbursement is sought.	We have replaced [redacted]
Pages 9, 10 and 13 the ERG state: *"The ERG identified significant technical errors within both original and updated models provided by the company, thereby limiting ERG ability to validate the results provided and undertake additional scenario and sensitivity analyses"* However in the later critique of the economic analysis in page 182 they state that they did not find any errors that would have a meaningful impact on deterministic model outputs.	Please amend this wording as follows: *"The ERG identified ~~**significant**~~ technical errors within both original and updated models provided by the company, thereby limiting ERG ability to validate the results **of scenario analyses and PSA** provided and undertake additional scenario and sensitivity analyses."*	The original description of "*significant technical errors"* suggests that the base-case results used in the analysis are not sound, however this is contradictory to the ERGs conclusions later in the report.	We appreciate the assumptions made via the use of the word "significant". We have amended the text to state the following: *"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."*
Pages 9, 10, 14 and 185 of the ERG report state: *"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*	Please amend this wording as follows: "*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*	The current statements are factually inaccurate. The secondary prevention HeFH population is also included in the base case result of the ASCVD population, for which CPRD was used to inform CV event rates.	Thank you. This was a repeated typographical error and the ERG have amended as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
company's base-case."	*company's **subgroup analysis**."*		
Page 12 of the ERG report Executive Summary states: *"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."* This statement does not mention that a sensitivity analysis was conducted which excludes ODYSSEY HIGH FH and produced results that were highly consistent with the base case.	Please amend this wording to the following: *"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 current statement contains missing details regarding the analyses provided by the company, and impact of this study on the NMA results. The current statement is misleading and as such, factually inaccurate.	We agree that this statement can be amended to improve clarity. As suggested we have amended as follows: *"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.**"*
1) Pages 8, 10, 12, 116 and 126 of the ERG report state: *"The ERG does not agree with company assumption that for the base-case analyses differences in*	Please amend this wording to the following: *"The ERG does not agree with company assumption that for the base-case analyses differences in*	The current statement wrongly implies that unobserved differences across the trials included in the NMA likely compromise the transitivity assumption.	We have discussed this issue and agree that the current statements contradict the later statement regarding transitivity assumptions in the company NMA. We are happy to rephrase this to highlight the

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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.	*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.***	As the ERG stated in page 157 of the ERG report "***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."*** Given this conclusion, the summary statement on page 12 is misleading and as such, factually inaccurate.	potential compromise of the transitivity assumption. We have added the following to the first point in all locations: ***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.***
2)Page 12, 116 and 126 of the ERG report also state: *"Inconsistencies in definitions and reporting of CV risk is likely to compromise the assumption of transitivity of the indirect treatment comparison."* The statement that inconsistencies in definitions of CV risk are likely to compromise the transitivity assumption suggests that it is certain that characteristics related to CV risk are known effect modifiers	***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***		We have amended the second point as follows in only two places, we did not find a third: ***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***

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
for the outcomes analysed and differences were observed across the included studies with regards to these factors. There is no strong evidence to suggest CV risk (aside from baseline LDL-C) is an effect modifier, nor were there significant differences observed across the trials at baseline for factors related to CV risk. Where differences were thought to be significant, sensitivity analyses were performed to exclude outlier trials, resulting in findings that were consistent with the base case.	***impact of CV risk on treatment efficacy, and may have compromised the assumption of transitivity."***		***compromised the assumption of transitivity.***
Page 21 of the ERG report states: "*Firstly, the overall mean serum LDL-C was 2.7mmol/L in the ORION trials (9, 10 and 11; CS B.2.3.6 p60, table 12)*."	Please review this sentence and revise it as applicable. The edit should make clear that the mean serum LDL-C was not calculated for the pooled analysis of the three ORION trials. The mean serum LDL-C for each arm of the three trials are presented in CS B.2.3.6 p60, table 12	The current statements are factually inaccurate.	We have amended this paragraph as follows: "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

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			similarities in baseline characteristics of the populations, and as no statistically significant differences were found between inclisiran and alirocumab in the CS NMA (**Error! Reference source not found.**), 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)."
Page 22 of the ERG report states: *"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*	Please review this sentence and revise it as applicable. The edit should make clear that bempedoic acid *received a negative ACD and therefore at the current time bempedoic acid cannot be considered an extremely pertinent comparator.*	The current statement is misleading and as such, factually inaccurate.	We acknowledge the comment made by the company regarding *GID-TA10534.* At the time of responding to FAC the final status of this appraisal is unknown, as per NICE's statement on their website: "Note that this document is not NICE's final guidance on this technology. The recommendations

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
in both prescription and uptake of inclisiran." *Bempedoic acid received a negative ACD following the committee meeting on 5th November 2020 and project documents are published on the NICE website since 11th December.*			in section 1 may change after consultation." We have changed the report text to the following" *"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."*
Page 23 of the ERG report states: *"The ERG is aware of the ongoing NICE appraisal of Ezetimibe (TA385 currently*	Please amend this wording as follows: *"The ERG is aware of the* ~~***ongoing***~~ *NICE appraisal of*	The current statement is factually inaccurate.TA385 was published in February 2016.	We have re-worded the statement on page 23 for clarity, as follows:

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paused).”	*Ezetimibe* ***(TA385 was published in February 2016).***		*“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).*
Page 34 of the ERG report states: “*The company also retrospectively applied a cut off date of 2015.*”	Please amend this wording as follows: “*The company also retrospectively applied a cut off date of 2015* ***to systematic literature reviews***.”	The current statement is misleading and as such, factually inaccurate.	We have amended as requested.
Page 34 of the ERG report states: “*Company restricted the search retrospectively to 2015 onwards*.”	Please remove this statement.	The current statement is factually inaccurate. The retrospective date limit was applied to systematic literature reviews only.	Statement changed to the following: “A retrospective date limit was applied to the systematic reviews only. The…”
Page 35 of the ERG report states: “*Appropriate assessment of titles and abstracts and full texts by two independent reviewers, with disputes between reviewers referred to a third reviewer, changed to one reviewer with second reviewer checking*.”	Please amend this wording as follows: “*Appropriate assessment of titles and abstracts and full texts by two independent reviewers, with disputes between reviewers referred to a third reviewer~~, changed to one reviewer with second reviewer~~*	The current statement is factually inaccurate. The only deviation came later during data extraction where it began with double data extraction, which was later changed to full extraction by one reviewer with second reviewer checking.	This statement has been removed.

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	~~*checking*~~."		
Page 35 of the ERG report states: "*Little information extracted for the comparator studies identified by the systematic literature review and included in the NMA*."	Please remove this statement.	The current statement is factually inaccurate. All comparator studies were fully data extracted to enable a thorough NMA feasibility assessment and subsequent NMA. The NMA data inputs was sent to the ERG during clarification.	This statement has been removed. We have updated the score to 'Yes' and add "Information extracted for the comparator studies identified by the systematic literature review and included in the NMA were provided by the company during clarification."

Page 35 of the ERG report states: *"CS states "A complete quality assessment in accordance with the NICE-recommended checklist for assessment of bias in RCTs is presented." The tool used in the CS deviated considerably from the Cochrane Risk of Bias Tool, with many of the signalling questions not addressed, and the domain 'Measurement of outcomes' not assessed at all in the CS. In addition, signalling questions (rather than domains) were rated for risk of bias."*	Please amend this wording as follows: "*CS states "Quality assessment of the RCTs was performed according to the criteria set out in the NICE user guide for company evidence submission (adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care)."*	The current statement is factually inaccurate. The tool used in the CS is the table in section 2.5.4 of the 'Single technology appraisal: User guide for company evidence submission template'. This tool is adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).	The comment requires further explanation. The tool used by the company (Table 14 Appendix D) is the minimum requirement provided by NICE in the NICE user guide for company evidence submission (adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care) taken from the 2014 guidance. The ERG independently assessed the included studies using the Cochrane risk of bias tool as recommended in the preferred NICE checklists updated in 2020. https://www.nice.org.uk/process/pmg20/resources/appendix-h-appraisal-checklists-evidence-tables-grade-and-economic-profiles-pdf-8779777885. In the text we have removed the comment regarding deviating and have rephrased this section to the following: **"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

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			assessed using the NICE preferred checklist, Cochrane risk of bias tool which included additional signalling questions and overall ratings for each domain.[20]"
Page 37 of the ERG report states: "*Briefly, the inclusion criteria were English-language 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."*	Please amend this wording as follows: "*The inclusion criteria were ~~English-language~~ 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 current statement is factually inaccurate. There was no language limit applied to the search.	Thank you, this has been updated in the text.
Page 39 of the ERG report states: "*Furthermore, a date limit of 2015 was applied to all abstracts and SLRs*."	Please amend this wording as follows: "*Furthermore, a date limit of 2015 was applied to all ~~abstracts and~~ SLRs*."	The current statement is factually inaccurate. The retrospective date limit was applied to systematic literature reviews only.	We have removed this from the text as requested.
Page 40 of the ERG report states: "*The company does not state if the RoB assessment was performed by two independent reviewers*."	Please remove this statement.	The current statement is factually inaccurate As stated in Appendix D1.8 *"During data extraction, two researchers independently conducted quality assessment for*	We have amended the statement to the following: The company state that two

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		each included study, at study level."	researchers independently conducted quality assessment for each included study, at study level (CS Appendix D1.8).
Page 51 of the ERG report states: *"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 2034."*	Please amend this wording as follows: "*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***."	The current statement is factually inaccurate.	We have amended this typographical error to 2034.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 52 of the ERG report states: *"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 510."*	Pease amend this wording 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***."	The current statement is factually inaccurate.	We have amended this typographical error to 540.
Table 7 on Page 56 of the ERG report states: *"6.8 (2.3, 10.6) as the placebo-group percentage change in LDL-C from baseline to day 510 in sensitivity 3: ANCOVA."*	Please amend this figure as follows: "*6.8 (****3.0****, 10.6)*"	The current figure is factually inaccurate.	We have amended this typographical error to "6.8 (**3.0**, 10.6)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 62 of the ERG report states: *"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 37.2% to 50.2% (p<0.001 for all time points)."*	Please amend this wording as follows: "*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**)."*	The current statement is factually inaccurate.	We have checked this data against those reported on page 73 of the CS document B which states "*37.2% to 50.5% (observed valued, p<0.0001 for all time points)*." We have changed the text in the report as we expect that the data provided by the company during the FAC is the correct data (***39.1% to 50.5%)***. We have also added "**up to Day 540**".
Table 9 on page 63 of the ERG report states: *"44 (18.9) as the placebo-group proportion of patients who attain global lipid targets for their level of ASCVD risk."*	Please amend this figure as follows: "*44 (**18.4**)*"	The current figure is factually inaccurate.	We have amended this typographical error to "44 (**18.4**)".
Table 12 on page 67 of the ERG report states: *"369 (99.2) as the reduction in LDL-C from baseline at any visit (responders) for the inclisiran group in ORION-9."*	Please amend this figure as follows: "***239** (99.2)*"	The current figure is factually inaccurate.	This typographical error has been amended to "**239** (99.2)".

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 68 of the EGR report states: [redacted]	Please amend this figure as follows: [redacted]	The current figure is factually inaccurate and there is a typographical error.	Thank you for your comments. These figures have been updated in the report.
Page 120 of the ERG report states: *In ORION-11, this accounted for 804/87 patients in the placebo arm and 811 patients in the inclisiran group.*	Please amend this figure as follows: *In ORION-11, this accounted for **804/807** patients in the placebo arm and 811 patients in the inclisiran group.*	The current figure is factually inaccurate.	The ERG have amended this typographical error as proposed.
Page 130 of the ERG report states: *"In the ASCVD population, inclisiran is* [redacted]	Pease amend this wording as follows: *"In the ASCVD population, inclisiran is* [redacted]	[redacted]	Thank you for your comment. The ERG have amended as proposed.
Page 130 of the ERG report states: *"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*	Please amend this wording to the following: "*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*	The current statement is misleading and as such, factually inaccurate.	Thank you for highlighting the Embase indexing guide and providing selected points extracted from the guide. However, it remains ERG opinion that MEDLINE and Embase should be searched separately for

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
for natural language terms/synonyms in the title and abstract fields were included and although it appears only Embase indexing terms were used, mapping to MeSH terms for MEDLINE is assumed to have occurred." Embase indexing guide mentions that more than 3,300 of the 5,200 journal titles currently indexed for MEDLINE are independently indexed for Embase for Elsevier. For articles from another 1,800 MEDLINE titles (with a focus on basic biomedicine, Allied Health and other topics that are peripheral to the core topics of Embase), MeSH indexing terms are mapped to Emtree to provide an index that is compatible with the Elsevier indexing. For MeSH sub headings: many are also found in Emtree, where this is not the case, or when the definition is slightly different, appropriate translation is made.	*embase.com, but note that searches for natural language terms/synonyms in the title and abstract fields were included ~~and although it appears only Embase indexing terms were used, mapping to MeSH terms for MEDLINE is assumed to have occurred~~*"		transparency, reproducibility and comprehensiveness, and that if they are searched simultaneously, all the relevant terms from both Emtree and MeSH should be included in the search. The current Cochrane handbook supports this view. This extract is taken from '2.2.2. Searching MEDLINE and Embase: specific issues' in the technical supplement to chapter 4 "In addition, a recent study found that records from MEDLINE were not always retrieved when searched through Embase due to MeSH not being available in Embase (Bramer et al 2017a). Although it is, therefore, technically possible to search across all MEDLINE records in Embase (note, not all PubMed records), it is recommended that both databases be searched separately." We have amended the text slightly to say '…and although it appears only Embase indexing terms were used, some mapping to MeSH terms for MEDLINE will have occurred'

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 135 of the ERG report states: "*Partially - company reports 'incremental' results with comparison to the base-case, rather than ranked incremental results, but provided ICERs versus the baseline and also full ICERs."*	Pease amend this wording as follows: "***Yes** - company reports 'incremental' results with comparison to the base-case, ~~rather than ranked incremental results~~, **and** provided ICERs versus the baseline and also fully incremental cost-effectiveness estimates*. "	The current statement is factually inaccurate as fully incremental cost-effectiveness results (ICERs) were provided in Table 82-84 and in all tables of sections B.3.8 and B.3.9 of the CS.	The ERG has amended the text to the following: "***Yes** - company reports 'incremental' results with comparison to the base-case, ICERs versus baseline and fully incremental cost-effectiveness estimates*."
Page 146 states that the mean LDL-C of the Beliard 2018 population at baseline was 8.0 mmol/L, however the source of this figure is unclear. The paper states a mean LDL-C at final clinic visit of 144 mg/dL (3.7 mmol/L), and maximal total cholesterol of 420 mg/dL (10.9 mmol/L). The ERG go on to conclude that the Beliard paper shows that patients exhibit lower event rate despite higher LDL-C than in the Mohrschladt analysis.	The source of this figure should be clarified, or else the figures corrected. If the figures are updated, the ERG should also adjust their conclusions accordingly.	If the ERG are seeking to use these figures, correctly ascertaining this value will be important for accuracy of any further scenario analyses future results.	Thank your comments. The ERG agrees with the company regarding the erroneous figure quoted for mean LDL-C levels. The ERG have revised the two corresponding paragraphs to discuss the population within the Beliard 2018 study with a mean LDL-C level of 3.7mmol/L (at final clinic visit). The ERG has also revised its conclusions in accordance with this.
Page 145 and 146 the ERG reports an event rate of 135 events per 1000 patient years for all events from Beliard 2018, however, it is unclear how this figure was arrived at from	Please amend this to 90 events per 1000 patient years (out of 511 recurrences), or clarify the source of this figure. Novartis has been unable to locate the source of the 135 value	The ERG are seeking to use these figures for scenario analyses, thus correctly ascertaining this value will be important for accuracy of future results.	The ERG have amended this to 90 as proposed. (table 27 and page 142)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
the paper.			
Page 147 of the ERG report states: *"However, both non-fatal CV event rates and CV death rates were lower than those in Mohrschladt (135 v 143 per 1000 patient years and 1.4 v 12 per 1000 patient years, respectively)."*	Please amend the figure as follows or clarify the source of this figure: *"However, 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)."*	The ERG are seeking to use these figures for scenario analyses, thus correctly ascertaining this value will be important for accuracy of future results.	Thank you for your comment. The ERG have amended as proposed.
Page 168 of the ERG report states: [redacted] Page 184 of the ERG report states: [redacted]	Please amend this wording as follows: [redacted] [redacted]	The current figure is factually inaccurate and the wording is unclear.	Thank you for your comment. The ERG has amended as proposed. The ERG has amended as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 174 of the ERG report states: "The scatterplot shows that there was some uncertainty around total costs and less so for the total costs. "	Please amend the figure as follows: "The scatterplot shows that there was some uncertainty around total **QALYs** and less so for the total costs. "	The current statement is factually inaccurate.	The ERG has amended as proposed.
Pages 129 and191 of the ERG report state: [redacted]	Please amend the figure as follows: [redacted]	For accuracy and clarity.	The ERG has amended as proposed in both locations.

Issue 2 General errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
Page 9 of the ERG report states: *"Technical errors in the model prohibited the ERG conducting scenario analyses with alternative data sources to establish the"*	Please amend this wording as follows: "*Technical errors in the model prohibited the ERG conducting scenario analyses with alternative data sources to establish the* ***impact on the base-case ICER***."	The sentence is not finished.	The ERG has completed the sentence as proposed.
Page 10 and 11 of the ERG report state: • *"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*	Please amend this wording and formatting as follows: • "*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*	The formatting is unclear and the comparisons are unfinished.	Thank you for your comment. The ERG has amended as proposed.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
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* • *Higher post-CV event health state management costs* *No difference in adverse event costs which were not included in the model"*	*CV events, when compared with alirocumab and evolocumab.* o *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:* o *Lower unit price (than other lipid lowering therapies (LLT) at list price)* o *Higher administration costs* ***(than other lipid lowering therapies (LLT) at list price)*** o *Higher post-CV event health state management costs*		

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
	than alirocumab and evolocumab at list price o *No difference in adverse event costs which were not included in the model, **when compared with other lipid lowering therapies (LLT)**.*		
Page 12 of the ERG report states: "*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*."	Please amend this wording as follows: "*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 current statement is ambiguous.	We have changed this as requested.
Page 12 of the ERG report Executive Summary states: *"ORION-10 and ORION-11 were pooled in the NMA based on the similarity between baseline*	Please amend this wording to the following: *"ORION-10 and ORION-11 were pooled in the NMA based on the similarity between baseline*	The current statement is not clearly described and may result in confusion.	We have amended the text as requested to add the following

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
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." This statement is unclear as described. We believe that this refers to comments in 2.3.1 Inclisiran Comparator Studies (page 68 of the ERG report) wherein it was suggested to assess the impact of differences between ORION-10 and ORION-11 by performing a sensitivity analysis that did not pool ORION-10 and ORION-11.	*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.****"*		***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.***
Page 21 of the ERG report states: "*However, though in agreement with adults who are primary prevention with elevated risk despite maximally tolerated statins but these threshold may be less suitable if patient LDL-C levels have improved significantly where the CVD risk score is usually used to assess benefits*. " The sentence is unclear and ambiguous. Additionally, adults who are primary prevention with elevated risk may be categorised as such due	Please review this sentence and revise it as applicable. The edit should make clear of the direction of the threshold and acknowledge the composition of the population of patients who are primary prevention with elevated risk.	The current statement is misleading and as such, factually inaccurate.	We have removed this statement from the report to improve clarity of the paragraph.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
to their FH or diabetes status.			
Page 21 and 139 of the ERG report state: "*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 anticipated marketing authorisation of inclisiran. These include high risk and very high risk patients (either on statins or are statin intolerant, with or without other lipid lowering therapies) with LDL-C targets of <1.8 mmol/L and <1.4 mmol/L respectively (as outlined in ESC/EAS guidelines[10]) and primary HeFH patients with LDL-C <2.6mmol/L"*	Please review this sentence and revise it as applicable. The edit should make clear that there is a difference between LDL-C threshold and targets. Patients with a baseline LDL-C of 2.6 mmol/L will be able to reach the lowest target of 1.4 mmol/L with inclisiran.	The current statement is misleading and as such, factually inaccurate.	Thank you for your comment, this has been amended in the text in both places to the following "*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* p*atients 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."*
Page 68 of the report states : *"Therefore the results from the ORION-9 and ORION-10 trials may not generalise to UK patients, particularly trial data on adults with a history of HeFH without ASCVD who were not included within this trial."*	It is not clear to the reader what "*this trial*" refers to – if it refers to ORION-10 please state. If it refers to results from ORION-9 this is a factual inaccuracy as ORION-9 did include adults with a history of HeFH without ASCVD.	The current statement is misleading and as such, factually inaccurate.	We have amended this text to improve clarity to the following **"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**

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
The ORION-9 trial included adults with a history of HeFH without ASCVD.			**results may not generalise to this population"**
Page 87 and 125 of the ERG report state: [redacted]"	Please update this wording to include missing details and to remove typographical error: [redacted]"	For clarity and easier communication.The current statement contains missing details regarding the percentage reduction in LDL-C of inclisiran versus ezetimibe from the NMA results.	To improve the clarity of this statement we have amended as requested in both sections of the report.
First sentence in Section 3.1 page 128 of the ERG report states: "*Novartis undertook an economic to assess the cost-effectiveness of inclisiran compared to other lipid lowering therapies for treating people with hypercholesterolaemia"*	Please amend this wording as follows: "*Novartis undertook an economic* ***analysis*** *to assess the cost-effectiveness of inclisiran compared to other lipid lowering therapies for treating people with hypercholesterolaemia"*	For clarity and easier communication.	We have amended this in the report.
Figure 1 on page 136 is too large and part of the diagram is cut off.	Resize the diagram to include all relevant information.	In its current state, it is not possible to see the CV and non-CV death states on the model diagram.	We have added this Figure to a landscape page in order to not shrink the Figure too much.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
Page 189 of the ERG report: *"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 57)."* The ICER of [redacted] do not agree with the ICER presented in Table 58 i.e. [redacted]	Please amend this wording as follows: *"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 58**)."*	For accuracy and clarity.	The ERG have amended as follows: *"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 5**8**)."*

Issue 3 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 8 and 20 of the ERG report state: *"The population is narrower than the anticipated marketing authorisation as only hypercholesterolaemia patients with a serum LCL-C of ≥2.6mmol/L are considered."* Page 20 of the ERG report states: *"The population presented in this submission is narrower than the anticipated marketing authorisation as only hypercholesterolaemia patients with a serum LCL-C of ≥2.6mmol/L are considered."* *Page 54 of the ERG report states:* Page 86 of the ERG report states: *"Inclisiran demonstrated a statistically significant percentage reduction in LCL-C compared to placebo (mean difference: -57.4; 95% CrI: -66.8 to -47.6) and ezetimibe (mean difference: -32.1; 95% CrI: -44.9 to -19.1)."*	Please update this wording to remove typographical error: "*The population is narrower than the anticipated marketing authorisation as only hypercholesterolaemia patients with a serum **LDL-C** of **≥2.6 mmol/L** are considered."* Please update this wording to remove typographical error: "*The population presented in this submission is narrower than the anticipated marketing authorisation as only hypercholesterolaemia patients with a serum **LDL-C** of **≥2.6 mmol/L** are considered*." Please update this wording to remove typographical error:" *The absolute change in **LDL-C** from 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*	These are all the same typographical error (use of 'LCL' rather than 'LDL').	Thank you for your comments, these have all been amended.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 17 on page 103 of the ERG report states under NCT01288443: *"Aged 18 to 75 years excluding lactating women. LCL-C ≥ 100 mg/dL while receiving stable dose of atorvastatin 10, 20, or 40 mg daily or at least 6 weeks."* Page 124 of the ERG report states: *"The population is narrower than the anticipated marketing authorisation as only hypercholesterolaemia patients with a serum LCL-C of ≥2.6mmol/L are considered."* Page 127 of the ERG report states: *"Inclisiran demonstrated a statistically significant percentage reduction in LCL-C compared to placebo (mean difference: -57.4; 95% CrI: -66.8 to -47.6) and ezetimibe (mean difference: -32.1; 95% CrI: -44.9 to -19.1)."* Page 139 of the ERG report states: *"The population presented in this submission is narrower than the*	*value, and treatment-by-visit interaction (as clarified in question A15 of clarification responses)*." Please update this wording to remove typographical error: "*Inclisiran demonstrated a statistically significant percentage reduction in **LDL-C** compared to placebo (mean difference: -57.4; 95% CrI: -66.8 to -47.6) and ezetimibe (mean difference: -32.1; 95% CrI: -44.9 to -19.1)*." Please update this wording to remove typographical error: "*Aged 18 to 75 years excluding lactating women. **LDL-C ≥100 mg/dL** while receiving stable dose of atorvastatin 10, 20, or 40 mg daily or at least 6 weeks.*" Please update this wording to remove typographical error:		

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
anticipated marketing authorisation as only hypercholesterolaemia patients with a serum LCL-C of ≥2.6mmol/L are considered."	"*The population is narrower than the anticipated marketing authorisation as only hypercholesterolaemia patients with a serum **LDL-C** of **≥2.6 mmol/L** are considered*." Please update this wording to remove typographical error: "*Inclisiran demonstrated a statistically significant percentage reduction in **LDL-C** compared to placebo (mean difference: -57.4; 95% CrI: -66.8 to -47.6) and ezetimibe (mean difference: -32.1; 95% CrI: -44.9 to -19.1)*." Please update this wording to remove typographical error: "*The population presented in this submission is narrower than the anticipated marketing authorisation as only hypercholesterolaemia patient"s with a serum **LDL-C** of **≥2.6 mmol/L** are considered*."		

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 of the ERG report states: *"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."*	Please update this wording to remove typographical errors: "*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*."	For clarity.	We have amended as requested.
Misspelling of ezetimibe on pages 8 and 11 of the ERG report: *"The comparators listed differ from the NICE final scope and ezetamabie was better placed as an active comparator."*	"*ezetamabie"* should be corrected to *"***ezetimibe**". Please amend here and in any other instances.	For clarity. This is a typographical error.	We have amended as requested.
Page 11 of the ERG report states: *"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."*	Please update this wording to remove grammatical and typographical errors: "*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*."	For clarity.	We have amended as requested.
Pages 11 and 18 of the ERG report state: *"while the term "mixed lipidaemia" is*	Please update this wording to remove typographical error:	For clarity.	We have amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
used to describe a combination of increased levels of LDL-C and triglyceride levels, and decreased high-density lipoprotein (HDL-C).”	“*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).”*		
Page 12 and page 164 of the ERG report states: *“Inclusion criteria in the ORION trails were mostly identical except for disease history and serum LDL levels to reflect the indications in each trial”*	“*trails*” should be corrected to “***trials***”	For clarity.	We have amended as requested.
Page 23 of the ERG report states: *“This would place it as a comparator to inclicirin.”*	Please update this wording to remove typographical error: *“This would place it as a comparator to **inclisiran**.”*	For clarity.	We have amended as requested.
Page 33 of the ERG report states: *“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 no in much detail.”*	Please update this wording to remove typographical error: “*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*.”	For clarity.	We have amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 of the ERG report states: *"There was evidence that suboptimal processes were employed (e.g. some single reviewer data extraction with checking) and the methods described in the CS submission were followed."*	Please update this wording to remove typographical error: "*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*."	For clarity.	We have amended as requested.
Page 52 of the ERG report states: *"Time-adjusted absolute change in LDL-C from baseline after Day 90and up to Day 540 and the percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B and non-HDL-C."*	Please update this wording to remove spacing typographical error: "*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*."	For clarity.	We have amended as requested.
Page 52 of the ERG report states: *"ORION-11: MACE. And the proportion of patients in each group with any LDL-C reduction from baseline at any visit."*	Please update this wording to remove typographical error: "*ORION-11**: MACE, and the** proportion of patients in each group with any LDL-C reduction from baseline at any visit*."	For clarity.	We have amended as requested.
Page 54 of the ERG report states: *"The absolute change in LDL form baseline to Day 510 and percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo-B,*	Please update this wording to remove typographical error: "*The absolute change in **LDL-C** from baseline to Day 510 and percentage change from baseline to Day 510 in*	For clarity. This is a typographical error.	We have amended as requested.

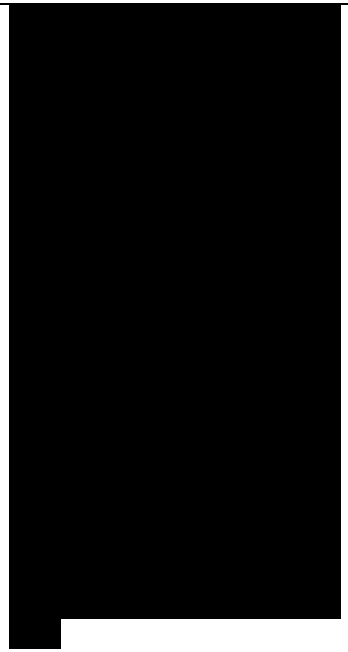
Description of problem	Description of proposed amendment	Justification for amendment	ERG response
and non-HDL-C was analysed using an MMRM with the following covariate: treatment, visit, baseline value, and treatment-by-visit interaction (as clarified in question A15 of clarification responses).”	*PCSK9, 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)*.”		
Pages 55 and 62 of the ERG report state: *“The results of the analyses of the key-secondary endpoints for all three ORION trials (9-, -10 and -11) are presented in ….”*	Please update this wording to remove typographical error: “*The results of the analyses of the key-secondary endpoints for all three ORION trials (**-9**, -10 and -11) are presented in …”*	For clarity. These are typographical errors.	We have amended as requested.
Misuse of the word invention at the top of page 67. *“Inventions were monotherapies or combination therapies of any of the following…..”*	Please update this wording to remove typographical error: “***Interventions** were monotherapies or combination therapies of any of the following…”*	For accuracy and clarity.	We have amended as requested.
Pages 55 and 62 of the ERG report state: “[redacted]”	Please update this wording to remove typographical error: “[redacted]”		We have amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 114 of the ERG report states: *"…the direct estimate for ezetimibe versus placebo from LAPLACE-2 was similar to the indirect RE NMA estimate (27.59 [-33.44, -21.75] vs. -22.4 [-30.7, -14.1], respectively)"*	Please update this figure to include negative sign before 27.59: *"…the direct estimate for ezetimibe versus placebo from LAPLACE-2 was similar to the indirect RE NMA estimate (**-**27.59 [-33.44, -21.75] vs. -22.4 [-30.7, -14.1], respectively)"*	For clarity. This is a typographical error.	We have amended as requested.
Page 129, the first sentence of the final paragraph is missing a closed parenthesis following [redacted]	[redacted]	For clarity.	We have amended as requested.
Sections 2.4 and 2.5 have the same heading.	Please rename the heading text for 2.4 or 2.5, or alternatively combine the sections.	For clarity	Thank you. We have renamed 2.5 to: "Summary of the network meta-analysis (NMA)"
Page 172 of the ERG report states: *"Results of the probabilistic sensitivity analysis are presented in Table 45 to Table 47."*	Please update this wording to remove typographical error: *"Results of the probabilistic sensitivity analysis are presented in **Table 43 to Table 45**."*	This is a typographical error.	We have amended as requested.
Page 172 of the ERG report states: *"The PSA results (Table 45) are in line with the deterministic results as shown in Table 46."*	Please update this wording to remove typographical error:	This is a typographical error.	We have amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	"*The PSA results **(Table 43)** are in line with the deterministic results as shown in **Table 40**."*		
Page 174 of the ERG report states: *"PSA results (Table 46) were in line with the deterministic results (Table 47) for the primary prevention with elevated risk population."*	Please update this wording to remove typographical error: *"PSA results **(Table 44)** were in line with the deterministic results **(Table 40)** for the primary prevention with elevated risk population."*	This is a typographical error.	We have amended as requested.
Page 186 of the ERG report states: *"The ERG identified negative values during cell checks but found these likely insufficient to effect model validity."*	Please update this wording to remove typographical error: *"The ERG identified negative values during cell checks but found these likely insufficient to **affect** model validity."*	This is a typographical error.	We have amended as requested.

Issue 4 Incorrect confidentiality marking

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>ERG response</th></tr>
<tr><td>Page 156, Table 31.</td><td>Company NMA results should be marked AiC.</td><td>
<table>
<tr><th rowspan="2">Intervention</th><th colspan="2">% LDL-C reduction from baseline to W 12 versus placebo</th></tr>
<tr><th>Toth et al.[23] abstract</th><th>Company NMA</th></tr>
<tr><td>Evolocumab (140mg Q2W)</td><td>-64.73 (-67.42, -62.03)</td><td>[redacted]</td></tr>
<tr><td>Alirocumab (150mg Q2W)</td><td>-62.71 (-67.56, -57.87)</td><td>[redacted]</td></tr>
<tr><td>Inclisiran (300mg)</td><td>-50.17 (-55.00, -45.35)</td><td>[redacted]</td></tr>
<tr><td>Ezetimibe (10 mg QD)</td><td>-24.64 (-27.68, -21.60)</td><td>[redacted]</td></tr>
</table>
</td><td>We have amended as requested.</td></tr>
<tr><td>Text in Section 2.5 describing the NMA is not marked AIC; examples include but are not limited to:
“[redacted]</td><td>Please mark Section 2.5 AIC as per the company submission.</td><td>This information is AIC; in the company submission the whole NMA section was marked AIC, except for:
Section B.2.9.2.1 (feasibility assessment)
Section B.2.9.4 (conclusions from the NMA)</td><td>We have amended as requested and added AIC marking to the NMA section. As expected, this has increased the AIC throughout our report.</td></tr>
</table>

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
			

NICE National Institute for Health and Care Excellence

Technical engagement response form

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm on 10 March 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Inclusion of ezetimibe as part of standard care rather than as active comparator	**YES**	**1. Clinical feedback on the use of ezetimibe in clinical practice in England** Novartis asked twelve primary care physicians, including General Practitioners (GPs) with an extended role in cardiology, about the use of ezetimibe in clinical practice in England. All agreed that ezetimibe is not used extensively in clinical practice. The key reasons were perceived weak evidence of effectiveness, patient resistance, and a perception of ezetimibe as a secondary care option (appropriate for patients who are intolerant to statins, with familial hypercholesterolaemia [FH] or with more challenging low-density lipoprotein cholesterol [LDL-C] management). Additional factors were a lack of incentives for LDL-C optimisation and a perceived gap between primary and secondary care. All experts (except one) reported very low ezetimibe prescribing (no more than 5% of patients receiving lipid lowering therapies), as evidenced by the patient share data discussed in part 2 below. One GP indicated more widespread use of ezetimibe but acknowledged that this is not the case nationally. Based on the feedback received, we believe our definition of standard of care as maximally tolerated statins with or without ezetimibe reflects real-world established NHS practice in England. Most GPs did not expect the use of ezetimibe to increase significantly. Key reasons were the lack of confidence in its efficacy and limited resources to manage lipid optimisation in primary care.

		The consensus of the primary care physicians, including a GP who is an advisor for NICE cardiology guidelines, was that ezetimibe is not a mandatory treatment step in the treatment pathway following inadequate response to maximally tolerated statins and prior to PCSK9 inhibitors. A more detailed summary of the primary care physicians' feedback is provided in Appendix 1. **2. Additional patient share data for ezetimibe and branded Ezetrol** The patient share for ezetimibe (generics) and Ezetrol (brand) combined has accounted for less than 3% of the dyslipidaemia market in England since 2015 (approx. 223,000-247,000 patient equivalents) [1]. Subnational data for England in 2020 indicates some variability in the usage of ezetimibe and Ezetrol across England, ranging from 0.5% up to a maximum of 4.9% patient share for both agents combined. In England in 2020, 50% of bricks (small geographical areas) reported a patient share between 2% and 3% for ezetimibe and Ezetrol combined; only 7% of bricks had a patient share of ≥4% for ezetimibe and Ezetrol combined [2]. Ezetimbe was launched in 2003, received a NICE recommendation in 2008 and a revision in 2016 and continues to be used in only a small minority of patients. Despite generic versions of ezetimibe being available since 2018, its usage has not dramatically increased in England. Year-on-year growth for ezetimibe generics and Ezetrol combined was 4.7% in 2019 and 2.7% in 2020. This is roughly in line with the growth seen across the entire dyslipidaemia market in 2019 and 2020 (~4% and ~2%, respectively) [1]. At this point in time, there are no foreseeable market events that would suggest this is likely to change. This is in stark contrast to when Zocor and Lipitor went generic in 2003 and 2012 respectively; the use of generics to Zocor (simvastatin) and Lipitor (atorvastatin) far exceeded the historic use of the respective branded products [3]. Furthermore, even rosuvastatin, which is a less frequently used statin in England, has witnessed 8-13% year-on-year growth following entry of generic versions of the molecule [1].

		3. Latest NICE guidelines Current NICE guideline CG181 includes ezetimibe as an option that can be considered but does not present it as a distinct step in the treatment pathway [4]. **4. Cost-effectiveness estimates including ezetimibe as an active comparator** Novartis is committed to bringing inclisiran to the market at a price that offers exceptional value versus the real-world standard of care (SoC). As confirmed by clinical experts, statins represent the mainstay SoC with a very small proportion of patients additionally receiving ezetimibe. We therefore continue to consider that our base case analysis, in which SoC is defined as maximally tolerated statins with or without ezetimibe, is the most appropriate for decision-making. However, in response to the ERG request to consider ezetimibe as an active comparator, we have provided scenario analyses in Appendix 2. These represent cost-effectiveness results that are relevant to the small proportion of patients who are receiving statins and ezetimibe in clinical practice. **<Commercial in confidence information removed>** Please note the proportion of ezetimibe usage within SoC in the cost-effectiveness model is informed by the ORION trials (c. 50-56%, 10% and 6-8% in ORION-9, -10 and -11, respectively [5-7]). This represents a conservative approach to the definition of SoC as ezetimibe usage in the trials was higher than current usage in UK clinical practice. **Conclusion** The guide to the methods of technology appraisal states that the Committee will normally be guided by established practice in the NHS when identifying the most appropriate comparator(s) [8]. Current NICE guideline CG181 demonstrates that ezetimibe is not an additional step in the treatment pathway [4]. Given the feedback from primary care physicians and the patient share data presented above, there is no reason to believe that ezetimibe usage will increase in the future. Considering the very low and somewhat variable current use of ezetimibe and that, based on the clinical feedback received, ezetimibe is likely to continue being used only for a very small minority of patients in the future, we believe our definition of SoC as maximally

		tolerated statins with or without ezetimibe reflects established clinical practice in the real-world. It is therefore the most suitable basis for decision-making on the cost-effectiveness of inclisiran.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Generalisability of the results from the ORION-10 and ORION-11 studies	Page 12	**NO**	Patient characteristics in the ORION trials are broadly comparable with patient characteristics in the CPRD study using the ARUM database (as presented in the submission), which contains records on approximately 13 million currently registered patients (23% of the total English population) (Table 1 and Table 2). There are some discrepancies (e.g. the proportion of diabetic patients), but the forest plots presented in the submission and the ORION trial publications demonstrate the **constant effectiveness of inclisiran** across subgroups, which provides reassurance regarding the generalisability of the ORION trials to the UK population.

Table 1: Patient characteristics in the ORION trials

Population		Age	% female	% diabetes	LDL-C (mmol/L)
Secondary prevention	ASCVD and serum LDL-C ≥2.6 mmol/L†	64.75	34%	38%	3.47
Primary prevention	PPER and serum LDL-C ≥2.6 mmol/L‡	62.28	54%	66%	4.02
	HeFH without ASCVD and serum LDL-C ≥2.6 mmol/L¶	52.36	58%	7%	4.09

†Source: patients with ASCVD in ORION-10 and -11; ‡Source: patients with PPER in ORION-11; ¶Source: patients in ORION-9.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease;.LDL-C, low-density lipoprotein cholesterol; PPER, primary prevention with elevated risk.

Table 2: Patient characteristics in the CPRD study

Population		Age	% female	% diabetes	LDL-C
Secondary prevention	ASCVD and serum LDL-C ≥2.6 mmol/L	68.77	45%	16%	3.47
Primary prevention	PPER and serum LDL-C ≥2.6 mmol/L	65.73	33%	15%	3.63
	HeFH without ASCVD and serum LDL-C ≥2.6 mmol/L	52.62	64%	2%	4.75

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CPRD, Clinical Practice Research Datalink; LDL-C, low-density lipoprotein cholesterol; PPER, primary prevention with elevated risk.

Additional issue 2: lack of genetic testing results in some FH cases being missed	Page 21	**NO**	We fully agree that there is an issue with the lack of genetic testing in clinical practice. Our understanding, as confirmed by clinical experts, is that patients are often coded as having FH by GPs when FH is suspected; however, this is often never confirmed as genetic testing is not required. Therefore, the population of patients with FH in the CPRD study is likely an overestimate. Additionally, there is no distinction in the CPRD database between homozygous and heterozygous FH (HeFH). This leads to heterogeneity within the cohort labelled as FH in the CPRD study and hence uncertainty in their CV event rates.

<table>
<tr><td></td><td></td><td></td><td>Additionally, patients with FH would also be classified into the other two population groups (i.e. primary prevention with elevated risk (PPER) or ASCVD). Our submission explains that the groups are not mutually exclusive; patients with FH would fall into the PPER or ASCVD category based on whether they have experienced a cardiovascular (CV) event.</td></tr>
<tr><td>Additional issue 3: lack of a scenario analysis using event rates from Beliard, 2018 because of technical errors in the company’s economic model</td><td>Page 135</td><td>YES</td><td>The requested scenario analysis for the HeFH secondary prevention population is presented below.

Beliard 2018 reports the rate of recurrent CV events in patients with secondary prevention HeFH as 9 per 100 patient years [9]. Of 511 observed events there were 36 myocardial infarctions, 31 unstable angina, 76 peripheral arterial disease, 8 CV deaths and 30 strokes, with the rest being revascularisations. Table 3 presents the resulting annual event probabilities used in the model.

Table 3: Annual event probabilities calculated using Beliard 2018
<table>
<tr><th>MI</th><th>UA</th><th>Stroke</th><th>Revascularisation</th><th>CV death</th></tr>
<tr><td>0.00632</td><td>0.005445</td><td>0.00527</td><td>0.056465</td><td>0.001408</td></tr>
</table>
Abbreviations: CV, cardiovascular; MI, myocardial infarction; UA, unstable angina.

The mean age of patients in the study was 60. No baseline LDL-C is reported, however, a mean LDL-C of 144 mg/dL is reported as the mean final value at last clinic visit; this was used to inform the model.

Results using Beliard 2018 to inform baseline CV event rates in the HeFH secondary prevention population are presented in Table 4. <Commercial in confidence information removed> Ezetimibe was not included in this analysis as it was not possible to include ezetimibe in the NMA for HeFH, due to an absence of data on ezetimibe’s efficacy in this population (Company submission Appendix D).</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
Table 4: Cost-effectiveness results in secondary prevention HeFH using Beliard 2018 event rates
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incr. costs (£)</th><th>Incr. LYG</th><th>Incr. QALYs</th><th>ICER versus baseline (£/QALY)</th><th>ICER incr. (£/QALY)</th></tr>
<tr><td>SoC</td><td colspan="8" rowspan="4"><Academic and commercial in confidence information removed></td></tr>
<tr><td>Inclisiran + SoC</td></tr>
<tr><td>Alirocumab + SoC</td></tr>
<tr><td>Evolocumab + SoC</td></tr>
</table>
Abbreviations: HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SoC, standard of care.
</td>
</tr>
<tr>
<td>Additional issue 4: The impact of differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes</td>
<td>Page 107</td>
<td>YES</td>
<td>See Appendix 3</td>
</tr>
</table>

focused on changes in LDL-C, HDL-C, and discontinuations			
Additional issue 5. Request for SUCRA plots and treatment ranking	Page 109	**YES**	See Appendix 3
Additional Issue 6: Request for NMA scenarios wherein ORION-10 and ORION-11 were not pooled (i.e. separate analyses were conducted based on each inclisiran trial)	Page 16	**YES**	See Appendix 3

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Not applicable – the estimates are unchanged.

References

1. *Patient equivalent numbers derived from IQVIA C10 data cube, Hospital Retail Combined Trawling Data, Yearly Unit Sales.* 2020.
2. *Patient shares derived from IQVIA C10 data cube, HPA Sub National Data, Monthly Unit Sales.* 2019-2020.
3. Chapman, S.R., R.W. Fitzpatrick, and M.I. Aladul, *Has cost inhibited the uptake of more potent statins in England?* Pharmacoepidemiology and Drug Safety, 2017. **26**(8): p. 984-991.
4. National Institute for Health and Care Excellence, *CG181: Cardiovascular disease: risk assessment and reduction, including lipid modification. Available at: https://www.nice.org.uk/guidance/cg181 (last accessed 9th April 2020).* 2016.
5. Data on file [INC-DOF-007], *ORION-10 Clinical Study Report.*
6. Data on file [INC-DOF-008], *ORION-11 Clinical Study Report.*
7. Data on file [INC-DOF-006], *ORION-9 Clinical Study Report.*
8. National Institute for Health and Care Excellence, *PMG9: Guide to the methods of technology appraisal 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword (last accessed 8th March 2021).* 2013.
9. Béliard, S., F. Boccara, B. Cariou, A. Carrié, X. Collet, M. Farnier, et al., *High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: The French Familial Hypercholesterolemia Registry.* Atherosclerosis, 2018. **277**: p. 334-340.

Novartis asked twelve primary care physicians, including General Practitioners (GPs) with an extended role in cardiology, about the use of ezetimibe in clinical practice in England. The questions asked are numbered below.

1. Why is ezetimibe not used more often?

All advisors agreed that ezetimibe is not used extensively in clinical practice for several reasons:

Perceived weak evidence of effectiveness: There was a consensus that there is a lack of belief in the conflicting evidence regarding the efficacy of ezetimibe. Historically, the PROVE-IT study and extension reported cardiovascular (CV) outcome results were marginal using ezetimibe. Despite publication of the IMPROVE-IT trial (which found ezetimibe reduces CV mortality, major CV event and non-fatal stroke), some clinical commissioning groups, as recently as 2020, have actively discouraged the use of ezetimibe on the grounds that the evidence is not strong enough. One advisor noted that, as a result, use of ezetimibe may be considered by many health care providers as a decision for specialists.

Patient resistance: It was also noted that usage is low as ezetimibe is usually only prescribed for secondary prevention in patients with uncontrolled cholesterol (and/or the patient cannot tolerate statins). In addition, patient resistance may be a contributing factor, as many are resistant to taking statins, and ezetimibe is an unknown drug to them. One clinician remarked that consult times are not long enough to convince patients otherwise, and instead lifestyle advice is reiterated.

Ezetimibe is seen as a secondary care option: It was noted that ezetimibe may be prescribed more frequently in secondary care lipid clinics. These clinics manage patients with FH or more challenging and/or CV event patients, representing a 'clinically different' pool, who require a more aggressive approach. Within primary care, one GP considered that ezetimibe would only be prescribed in rare cases where a consultant mentions addition of ezetimibe for a specific patient to achieve a certain cholesterol target. Another cardiology GP reported that despite encouraging primary care network colleagues to consider ezetimibe in some patients, this was met with resistance as they do not see a clear place for its use. Amongst those GPs who do see a role for ezetimibe, itis largely seen as being for patients who are intolerant to statins. Additionally, very high-risk patients, such as patients with familial hypercholesterolaemia (FH), are seen as potentially appropriate for ezetimibe, but these patients are not always on the radar of GPs and many remain undiagnosed.

Gap between primary and secondary care: The clinicians also agreed that ezetimibe falls into the gap between primary and secondary care. Often, hospital consultants start patients on secondary prevention medicines and transfer lipid lowering therapy (LLT) management to the primary care physician without explicit instructions; most will use 'fire and forget' statins.

Lack of incentives for LDL-C optimisation: The primary care system does not adequately reward LDL-C optimisation; thus, it is not a primary concern for many GPs. The NICE Quality and Outcomes Framework only incentivises a total cholesterol of 5 mmol/L or less. Several of the clinicians suggest that only a national change in policy/restructuring of healthcare systems delivery (such as increased investment and incentives) and an increase in cardiologists requesting specific follow-up will increase use of secondary prevention medicines such as ezetimibe.

2. **In those exceptional cases where it is prescribed, what characterises these patients?**

There was a consensus that ezetimibe is usually prescribed either by a lipid optimisation service, a GP with an extended role in cardiology, or a motivated health care practitioner who has had a major influence on the local service and patient pathway. Primary care physicians agreed ezetimibe could be used as an additional therapy for secondary prevention in high-risk patients, including those with FH, or who are either statin intolerant or have persistently high cholesterol levels despite maximum statin therapy; this would usually be following advice from secondary care. There were conflicting reports regarding ezetimibe monotherapy, with some clinicians noting ezetimibe should not be prescribed to patients as a single therapy, however a cardiology GP stated that some non-cardio specialist GPs may use it in cases of true statin intolerance or patient refusal of statins as, although there is weak evidence, they consider it 'better than nothing'.

3. **How many patients a month do you see with primary hypercholesterolemia (heterozygous-familial* or non-familial)? Out of these patients, how many are receiving the below medicines (overlap in use is acceptable)?**
    - **Statins**
    - **PCSK9 inhibitors**
    - **Ezetimibe**

One GP with an extended role in cardiology reported seeing 100 patients on LLT per month. Other GPs reported seeing between five to 20 patients with elevated LDL-C per month. All GPs noted that most or all these patients received stains, while zero received PCSK9 inhibitors. In general, few patients are prescribed ezetimibe: one GP reported prescriptions for 3–5% patients on LLT seen per month, another 110 out of 17,000 practice patients, another 50 out of 6,500 practice patients and another in a maximum of 5% of patients seen. In contrast, one GP indicated more widespread use of ezetimibe amongst 'not at target' patients but acknowledged that this is not the case nationally.

4. **Over the next 3 years, do you anticipate the use of these medicines in clinical practice will increase, decrease, or remain the same and if so by how much?**
    - ***Statins***
    - ***PCSK9 inhibitors***
    - ***Ezetimibe***

Most GPs did not expect the use of ezetimibe to increase significantly. Key reasons were the lack of confidence in its efficacy and limited resources to manage lipid optimisation in primary care.

The consensus was that the use of statins is likely to increase over the next three years. A variety of reasons were suggested, including:

- The more sedentary lifestyle adopted by patients during lockdown,
- Projects currently in development that aim to improve cardiovascular disease prevention and pushing primary prevention more,
- The new NICE Rapid Uptake Product (RUP) guidance.

It was suggested that the RUP guidance may also increase the use of PCSK9 inhibitors and inclisiran (following NICE decision). Another GP also predicted an increase in PCSK9

inhibitors if referral pathways to specialist services are unblocked and more patients get access.

Contrastingly, one clinician did not expect any changes in statin use but predicted an increase of 10–20% (best case scenario) in the use of ezetimibe. Another stated that the use of ezetimibe appears to be increasing slowly but acknowledged that this may not be the case elsewhere.

5. **Do you believe ezetimibe to be a <u>mandatory</u> treatment step with/after initial statin therapy?**

The consensus of the primary care physicians, including a GP who is an advisor for NICE cardiology guidelines, was that ezetimibe is not a mandatory treatment step in the treatment pathway following inadequate response to maximally tolerated statins and prior to PCSK9 inhibitors.

Two clinicians noted that they do not wish to see ezetimibe as a mandatory step, with one suggesting that ezetimibe could delay referral for patients who require PCSK9 inhibitors. Another GP stated that although it is not mandatory, they would not refer a patient to a lipid specialist without having tried ezetimibe first.

Results of the scenario analyses with ezetimibe as an active comparator

Tables 18, 19 and 20 highlighted in green have been updated after we've realised there was an error in selecting the appropriate efficacy data in the model for the statin intolerant population and an error in the Risk mapping from CPRD for the very high risk population.

Results for this scenario analysis were presented in our responses to clarification question A14. We have reported them again below.

Table 1 and Table 2 present the cost-effectiveness estimates including ezetimibe as an active comparator in ASCVD and PPER. In this analysis ezetimibe has been excluded from SoC and patients on ezetimibe in the ORION studies do not inform the baseline characteristics of the modelled cohort. Results for primary prevention HeFH patients are not presented as it was not possible to include ezetimibe in the NMA for HeFH, due to an absence of data on ezetimibe's efficacy in this population (Company submission Appendix D), though the PPER population will include patients with HeFH. Similarly no results have been presented for the secondary prevention HeFH group, however the ASCVD population does included patients with HeFH and a history of CV events.

When compared to ezetimibe + SoC, inclisiran produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in an ICER of [redacted]

Table 1: Base-case results ASCVD (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Results for the base-case analysis for the PPER population, using the inclisiran commercial agreement price, are presented in **Table 2**. When compared to ezetimibe + SoC, inclisiran produces an additional [redacted] QALYs with an incremental cost of [redacted], resulting in an ICER of [redacted]. [redacted]

Table 2: Base-case results PPER (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
Evolocumab+SoC	[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.

Sensitivity analyses incorporating ezetimibe + Soc in fully incremental analyses

ASCVD

Probabilistic sensitivity analysis

Joint parameter uncertainty was tested through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. The results of the PSA (Table 3) were found to be congruent with the base-case results (Table 1). [redacted]. Results were plotted on the cost-effectiveness plane (CEP; Figure 1) and a multiple cost-effectiveness acceptability curve (CEAC; Figure 2) was generated. [redacted]

Table 3: Results of probabilistic sensitivity analysis, ASCVD

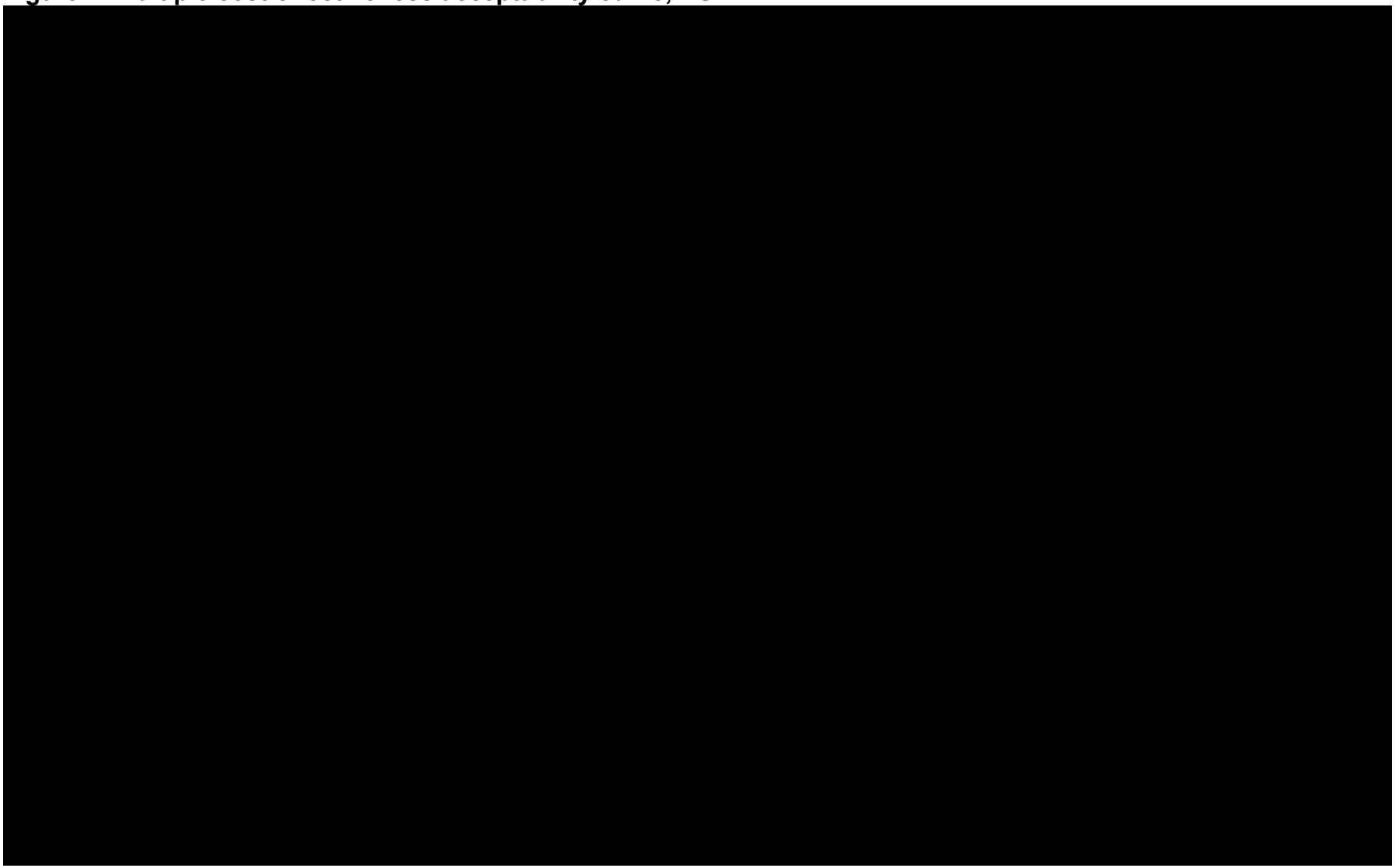
Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe+SoC	[redacted]	[redacted]	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 1: Scatterplot of PSA results, ASCVD

Abbreviations: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 2: Multiple cost-effectiveness acceptability curve, ASCVD



Abbreviations: SoC, standard of care.

Deterministic sensitivity analysis

Parameter uncertainty was tested using deterministic sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range determined by either the 95% CI, or ±15% where no estimates of precision were available. The results of deterministic sensitivity analysis are presented as a tornado diagram in **Figure 3**. [redacted]

Figure 3: Tornado diagram vs Ezetimibe+SoC, ASCVD

Abbreviations: SoC, standard of care.

Primary prevention with elevated risk

Probabilistic sensitivity analysis

Joint parameter uncertainty was tested through PSA, in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded. The results of the PSA (**Table 4**) were found to be congruent with the base-case results (**Table 2**). [redacted] Results were plotted on the CEP (**Figure 4**) and a multiple CEAC (**Figure 5**) was generated. [redacted]

Table 4: Results of probabilistic sensitivity analysis, PPER

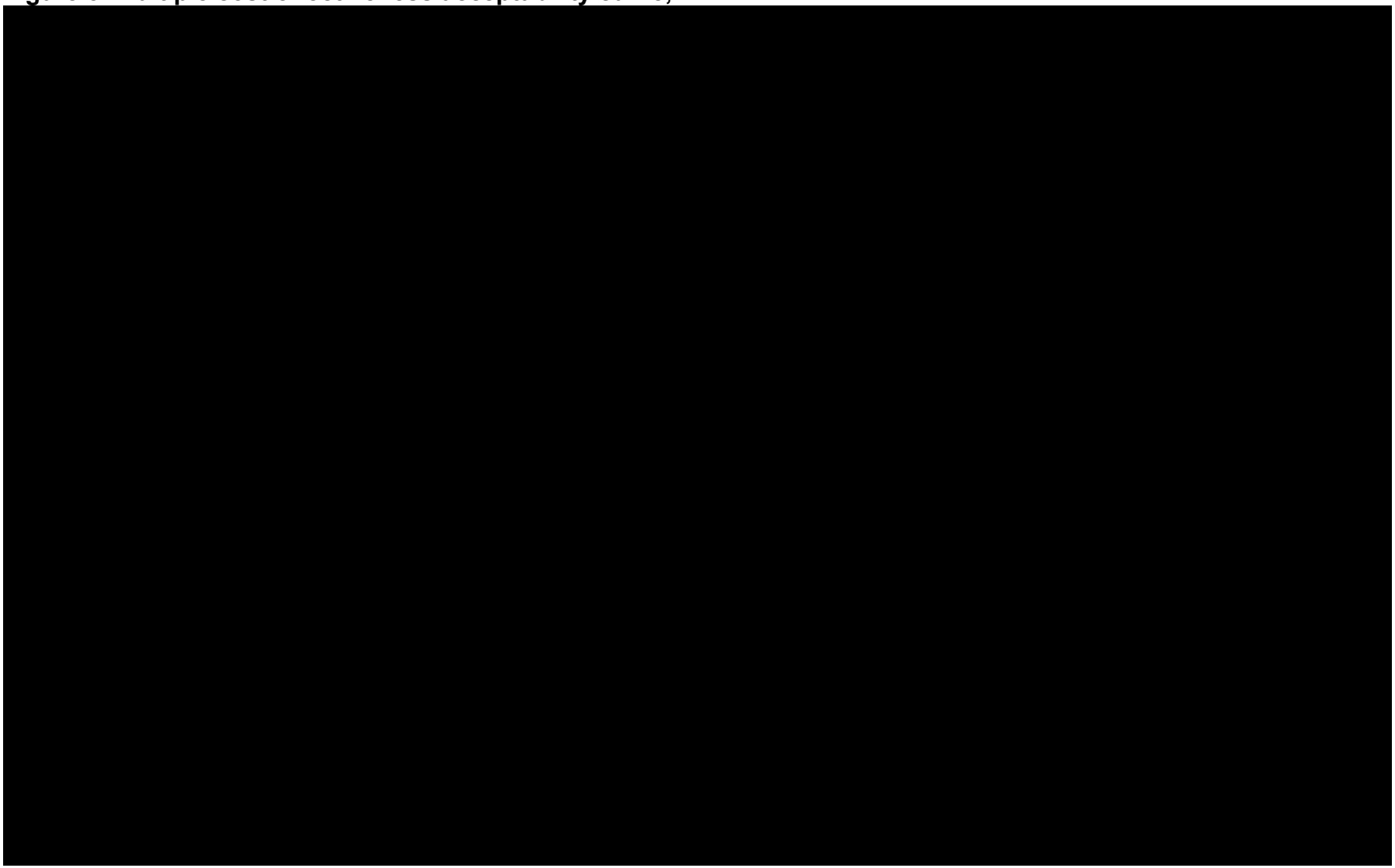
Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe+SoC	[redacted]	[redacted]	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 4: Scatterplot of PSA results, PPER

Abbreviations: QALY, quality-adjusted life-year; SoC, standard of care.

Figure 5: Multiple cost-effectiveness acceptability curve, PPER



Abbreviations:SoC, standard of care.

Deterministic sensitivity analysis

Parameter uncertainty was tested using deterministic sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range determined by either the 95% CI, or ±15% where no estimates of precision were available. The results of deterministic sensitivity analysis are presented as a tornado diagram in **Figure 6**. [redacted]

Figure 6: Tornado diagram vs SoC, PPER

Abbreviations: SoC , standard of care.

Scenario analysis

Equal efficacy for inclisiran and PCSK9is

The following analyses assume that PSCK9is have the same efficacy as inclisiran.

ASCVD

Table 5: Results in the ASCVD population assuming equivalent efficacy for inclisiran and PCSK9is

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

PPER

Table 6: Results for primary prevention patients with elevated risk assuming equivalent efficacy for inclisiran and PCSK9is

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Efficacy for inclisiran taken from the clinical trials

Here the time-adjusted difference between inclisiran and placebo from the pooled efficacy dataset (51.43%) for ASCVD and PPER is used, rather than data from the NMA.

ASCVD

Table 7: Results in the ASCVD population using inclisiran efficacy from the ORION clinical trial programme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

PPER

Table 8: Results for primary prevention patients with elevated risk using inclisiran efficacy from the ORION clinical trial programme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Adjusting rate ratios for CV events according to Collins et al

The following scenario explores the impact of removing the first year of treatment from the calculation of rate ratios for CV events.

ASCVD

Table 9: Results in the ASCVD population adjusting the CV event RRs per mmol/L change in LDL-C to remove the impact of the first year

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

PPER

Table 10 Results for primary prevention patients with elevated risk adjusting the CV event RRs per mmol/L change in LDL-C to remove the impact of the first year

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Including discontinuation of inclisiran and PCSK9is

This scenario explores the impact of discontinuation on cost-effectiveness, assuming patients discontinue all treatments at the same rate (5% per year).

ASCVD

Table 11: Results in the ASCVD population including discontinuation: Scenario 2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

PPER

Table 12 Results for primary prevention patients with elevated risk including discontinuation: Scenario 2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Including discontinuation of statin therapy

This scenario explores the impact of discontinuation of statin therapy on cost-effectiveness, with discontinuation rates taken from the ORION trials (Company Submission, Section B3.3.5.2). In the ASCVD and PPER populations the annual rate of discontinuation of statins is assumed to be 1.18%.

ASCVD

Table 13: Results in the ASCVD population including discontinuation of underlying statin therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

PPER

Table 14 Results for primary prevention patients with elevated risk including discontinuation of underlying statin therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Assuming inclisiran has no impact on LDL-C until day 90

The following scenario analyses assume that inclisiran has no impact on LDL-C until day 90.

ASCVD

Table 15: Results in the ASCVD population assuming no impact on LDL-C until day 90 for inclisiran

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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-car

PPER

Table 16 Results for primary prevention patients with elevated risk assuming no impact on LDL-C until day 90 for inclisiran

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Subgroup analysis

ASCVD

Severity of hypercholesterolemia

Table 17 presents the results for patients with ASCVD and serum LDL-C ≥4.0 mmol/L, reflecting one of the populations in which alirocumab and evolocumab are recommended.

Table 17: Results for patients with ASCVD and serum LDL-C ≥4.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Table 18 presents the results for patients with very high risk of CVD and LDL-C ≥3.5 mmol/L.

Table 18: Results for patients with very high risk of CVD† and serum LDL-C ≥3.5mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).

Statin intolerant

Statin intolerant patients in ORION-10 & -11 had higher baseline LDL-C than the overall ASCVD (4.17mmol/L vs 3.45mmol/L). The SoC arm in this population excludes both statins and ezetimibe and thus assumes patients are untreated. In the ORION-10 and -11 data used to inform the baseline characteristics for this population, 67% of patients were untreated and 33% were using LLT other than statins or ezetimibe, including fibrates, fish oil and docosahexaenoic acid, however the cost of these therapies has not been included in the model.

Table 19: Results for statin intolerant patients with ASCVD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

PPER

Statin intolerant

Statin intolerant PPER patients in ORION-11 had higher baseline LDL-C than the overall PPER population (5.00 mmol/L vs 4.02 mmol/L). In the ORION-11 data used to inform the baseline characteristics for this population, 84% of patients were untreated and 16% were using LLT other than statins or ezetimibe, including fibrates, fish oil and docosahexaenoic acid, however the cost of these therapies has not been included in the model.

Table 20: Results for primary prevention patients with elevated risk who are intolerant to statins

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Additional issue 4: The impact of differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations

<Academic in confidence information removed>

Table 1. Results of NMA Meta-Regression for ASCVD/RE Network – % Change in LDL-C at 24 Weeks – inclisiran versus Other Treatments

Comparator	Difference in % CFB (95% CrI)	Probability Inclisiran is Better
Base case		
Alirocumab	**<Academic in confidence information removed>**	
Evolocumab		
Ezetimibe		
Placebo		
Meta-regression adjusting for Baseline LDL-C		
Alirocumab	**<Academic in confidence information removed>**	
Evolocumab		
Ezetimibe		
Placebo		

Additional issue 5: Request for SUCRA Plots and Treatment Ranking

<Academic in confidence information removed>

Figure 1. SUCRA for NMA Base Case Network for ASCVD/RE population on MTD Statin – % Change in LDL-C at 24 Weeks

<Academic in confidence information removed>

Figure 2. SUCRA for NMA Base Case Network for ASCVD/RE Statin Intolerant population – % Change in LDL-C at 24 Weeks

<Academic in confidence information removed>

Figure 3. SUCRA for NMA Base Case Network for HeFH population – % Change in LDL-C at 24 Weeks

<Academic in confidence information removed>

Additional issue 6: Request for NMA scenarios wherein ORION-10 and ORION-11 were not pooled (i.e. separate analyses were conducted based on each inclisiran trial)

<Academic in confidence information removed>

Table 2. Results of NMA Scenario Analyses Wherein ORION-10 and ORION-11 are Not Pooled – % Change in LDL-C at 24 Weeks – inclisiran versus Other Treatments

	ASCVD/RE on MTD Statin		ASCVD/RE and Statin Intolerant	
Comparator	**Difference in % CFB (95% CrI)**	**Probability Inclisiran is Better**	**Difference in % CFB (95% CrI)**	**Probability Inclisiran is Better**
Base case				
Alirocumab	**<Academic in confidence information removed>**			
Evolocumab				
Ezetimibe				
Placebo				
Exclude ORION-10				
Alirocumab	**<Academic in confidence information removed>**			
Evolocumab				
Ezetimibe				
Placebo				
Exclude ORION-11				
Alirocumab	**<Academic in confidence information removed>**			
Evolocumab				
Ezetimibe				
Placebo				

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Results for PCSK9i eligible and ineligible patients

Contents

Tables

For instructions on generating results please see the Appendix.

Novartis base-case (ezetimibe as part of SoC)

ASCVD

Full population

Table 1 and Table 2 present the cost-effectiveness results for inclisiran in the ASCVD population not eligible for treatment with PCSK9is, i.e. those with LDL-C ≥ 2.6 mmol/L but below 4 mmol/L, for the full population and the statin intolerant population respectively. In both cases there is a moderate increase in the ICER from the base-case, driven by the lower mean LDL-C levels for these populations when restricting to patients with LDL-C < 4 mmol/L.

Table 1: Results for patients with ASCVD, LDL-C ≥ 2.6mmol/L, <4.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.

Table 2: Results for patients with ASCVD, statin intolerant LDL-C ≥ 2.6mmol/L, <4.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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
[ł]SoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Table 3 and Table 4 present the results of the cost-effectiveness analysis in for patients with ASCVD that are eligible for PCSK9is, i.e. those with LDL above 4.0 mmol/L, in the full population and statin intolerant population respectively. Due to the increase in the mean LDL-C the ICERs decrease in both analyses versus the base case.

Table 3: Results for patients with ASCVD and LDL-C ≥4.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Table 4: Results for patients with ASCVD and LDL-C ≥4.0 mmol/L, statin intolerant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoCł	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Very high risk CVD

Table 5 and Table 6 present the results for the very high risk CVD cohort not eligible for PCSK9is, i.e. those with LDL-C above 2.6 mmol/L but below 3.5 mmol/L, for the full population and the statin intolerant population, respectively. Results for the very high risk CVD subgroup show an increase in the ICER from the base-case (ASCVD with a serum LDL-C ≥ 2.6mmol/L) when considering the population not eligible for PCSK9is despite higher baseline risks for this population. This is driven by the lower mean LDL-C levels for this population when restricting to patients with LDL-C < 3.5 mmol/L. Additionally, there are differences in the modelling approach applied for the two populations. The base case analysis in the full ASCVD population accounts for the heterogeneity of the baseline risks by patient history and adjusts risks based on event history, for example whether or not the index event was an ACS event, a stroke, or PAD. As the very high risk subgroup was only considered as a subgroup analysis for comparability with previous PCSK9is' submissions, the modelling approach within this population does not account for this heterogeneity or increase in risks with multiple events.

Table 5: Very high risk CVD†, LDL-C ≥ 2.6mmol/L, <3.5mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).

Table 6: Very high risk CVD†, statin intolerant LDL-C ≥ 2.6mmol/L, <3.5mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC‡	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).
‡SoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Table 7 and Table 8 present the results for the very high risk CVD subpopulation eligible for PCSK9is, i.e. those with LDL-C above 3.5mmol/L, for the full population and for statin intolerant patients. These analyses are in line with those presented in the original submission.

Table 7: Very high risk CVD† and LDL-C ≥3.5mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).

Table 8: Results for patients with very high risk of CVD† and LDL-C ≥3.5mmol/L, statin intolerant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC‡	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).
‡SoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

PPER

Table 9 and Table 10 present the base-case results for the PPER population, excluding the PCSK9is from the comparison as they are not recommended for this population. These results are in-line with those presented in the original submission.

Table 9: Base-case results PPER

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.

Table 10: Results for patients who are intolerant to statins, PPER

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Table 11 to Table 16 present the results for the PPER population, considering the full patient population and the statin intolerant patients, at upper thresholds of LDL-C of 4.0, 5.0 and 6.0mmol/L based on the ERG's suggestion communicated to Novartis on 24th March. The ICERs increase for these analyses compared to the base-case figures as the average LDL-C of the population decreases, and as the LDL-C threshold rises the ICER falls. In most analyses the ICER remains below £20,000/QALY, with the exception of the statin tolerant patients with an LDL-C below 4.0mmol/L, where the ICER is [redacted]/QALY. Given that PCSK9is are not currently recommended in the PPER population, it is unclear to Novartis why it is relevant to consider an upper limit for LDL-C.

Table 11: Results for the PPER population, LDL-C ≥2.6mmol/L, <4.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.

Table 12: Results for the statin intolerant PPER population, LDL-C ≥2.6mmol/L, <4.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Table 13: Results for the PPER population, LDL-C ≥2.6mmol/L, <5.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.

Table 14 Results for the statin intolerant PPER population, LDL-C ≥2.6mmol/L, <5.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Table 15: Results for the PPER population, LDL-C ≥2.6mmol/L, <6.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.

Table 16: Results for the statin intolerant PPER population, LDL-C ≥2.6mmol/L, <6.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Primary prevention HeFH

Table 17 and Table 18 present the cost-effectiveness results in the primary prevention HeFH population amongst patients not eligible for PCSK9is, i.e. those with LDL-C below 5.0 mmol/L, for the full population and statin intolerant subgroup respectively. It should be noted that the HeFH primary prevention population with LDL-C ≥2.6mmol/L, <5.0mmol/L, falls within the broader PPER population with LDL-C ≥2.6mmol/L, <5.0mmol/L (as described in the original submission (Sections B1.3.2.3 and B2.3.3.1).

Table 17: Primary prevention HeFH, LDL-C ≥2.6mmol/L, <5.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.

Table 18: Primary prevention HeFH, statin intolerant LDL-C ≥2.6mmol/L, <5.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Table 19 and Table 20 present the cost-effectiveness results in the primary prevention HeFH population amongst patients eligible for PCSK9is, i.e. those with LDL-C above 5.0 mmol/L, for the full population and statin intolerant subgroup respectively.

Table 19: Results for primary prevention HeFH patients with LDL-C ≥5.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.

Table 20: Results for primary prevention HeFH patients with LDL-C ≥5.0mmol/L, statin intolerant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

ERG base-case (ezetimibe as an active comparator)

ASCVD

Full population

Table 21 and Table 22 present the cost-effectiveness results for inclisiran in the full and statin intolerant ASCVD population not eligible for treatment with PCSK9is (i.e. those with LDL-C levels <4 mmol/L), respectively. In both populations, there was an increase in the ICER from the base case, which was driven by the lower mean LDL-C levels for these populations when analysing patients with LDL-C <4 mmol/L.

Table 21: Results for patients with ASCVD, LDL-C ≥2.6 mmol/L, <4.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
‡SoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 22: Results for patients with ASCVD, statin intolerant LDL-C ≥2.6 mmol/L, <4.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes other lipid lowering therapies and no treatment.

Table 23 and Table 24 present the results of the cost-effectiveness analysis in for patients with ASCVD who are eligible for PCSK9is, i.e. those with LDL above 4.0 mmol/L, in the full population and statin intolerant population, respectively.

Table 23: Results for patients with ASCVD and LDL-C ≥4.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoCł	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
łSoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 24: Results for patients with ASCVD and LDL-C ≥4.0 mmol/L, statin intolerant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoCł	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
łSoC for the statin intolerant population includes other lipid lowering therapies and no treatment.

Very high risk CVD

Table 25 and Table 26 present the results for very high risk CVD patients who are not eligible for PCSK9is, i.e. those with LDL-C ≥2.6 mmol/L but <3.5 mmol/L, for the full population and the statin intolerant population respectively.

Table 25: Results for patients with very high risk CVD†, LDL-C ≥2.6 mmol/L, <3.5 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).
‡SoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 26: Results for patients with very high risk CVD†, statin intolerant LDL-C ≥2.6 mmol/L, <3.5 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).
‡SoC for the statin intolerant population includes other lipid lowering therapies and no treatment.

Table 27 and Table 28 present the results for the very high risk CVD subpopulation eligible for PCSK9i, i.e. those with LDL-C >3.5 mmol/L, for the full population and for statin intolerant patients.

Table 27: Results for patients with very high risk of CVD† and LDL-C ≥3.5 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).
‡SoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 28: Results for patients with very high risk of CVD† and LDL-C ≥3.5 mmol/L, statin intolerant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).
‡SoC for the statin intolerant population includes other lipid lowering therapies and no treatment.

PPER

Table 29 and Table 30 present the results for the PPER population including ezetimibe as an active comparator, excluding the PCSK9is from the comparison, as they are not recommended for this population.

Table 29: Results for the full population, PPER

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
‡SoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 30: Results for patients who are intolerant to statins, PPER

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
‡SoC for the statin intolerant population includes other lipid lowering therapies and no treatment.

Table 31 to Table 36**Table 16** present the results for the PPER population, considering the full patient population and the statin intolerant patients, at upper thresholds of LDL-C of 4.0, 5.0 and 6.0mmol/L. These ICERs increase as the average LDL-C of the population decreases, and as the LDL-C threshold rises the ICER falls. In most analyses the ICER remains below £20,000/QALY, with the exception of the statin tolerant patients with an LDL-C below 4.0mmol/L, where the ICER is [redacted] QALY. Given that PCSK9is are not currently recommended in the PPER population, it is unclear to Novartis why it is relevant to consider an upper limit for LDL-C.

Table 31: Results for the PPER population, LDL-C ≥2.6mmol/L, <4.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoCł	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
łSoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 32: Results for the statin intolerant PPER population, LDL-C ≥2.6mmol/L, <4.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoCł	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes other lipid lowering therapies and no treatment.

Table 33: Results for the PPER population, LDL-C ≥2.6mmol/L, <5.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoCł	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
łSoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 34 Results for the statin intolerant PPER population, LDL-C ≥2.6mmol/L, <5.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoCł	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes other lipid lowering therapies and no treatment.

Table 35: Results for the PPER population, LDL-C ≥2.6mmol/L, <6.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoCł	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
łSoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 36: Results for the statin intolerant PPER population, LDL-C ≥2.6mmol/L, <6.0mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER vs SoC (£/QALY)	Incremental ICER (£/QALY)
Ezetimibe + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC[ł]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes other lipid lowering therapies and no treatment.

Primary prevention HeFH

Table 37 and Table 38 present the cost-effectiveness results in the primary prevention HeFH population amongst patients not eligible for PCSK9is, i.e. those with LDL-C below 5.0 mmol/L, for the full population and statin intolerant subgroup, respectively. It was not possible to include ezetimibe in the NMA for HeFH, thus it has not been included in these analyses and results do not differ from the company base-case. It should be noted that that the HeFH primary prevention population with LDL-C ≥2.6mmol/L, <5.0mmol/L, falls within the broader PPER population with LDL-C ≥2.6mmol/L, <5.0mmol/L (as described in the original submission (Sections B1.3.2.3 and B2.3.3.1).

Table 37: Primary prevention HeFH, LDL-C ≥2.6 mmol/L, <5.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
łSoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 38: Primary prevention HeFH, statin intolerant LDL-C ≥2.6 mmol/L, <5.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoCł	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Table 39 and Table 40 present the cost-effectiveness results in the primary prevention HeFH population amongst patients eligible for PCSK9is, i.e. those with LDL-C above 5.0 mmol/L, for the full population and statin intolerant subgroup, respectively.

Table 39: Results for primary prevention HeFH patients with LDL-C ≥5.0 mmol/L

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)	Incremental ICER (£/QALY)
SoCł	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

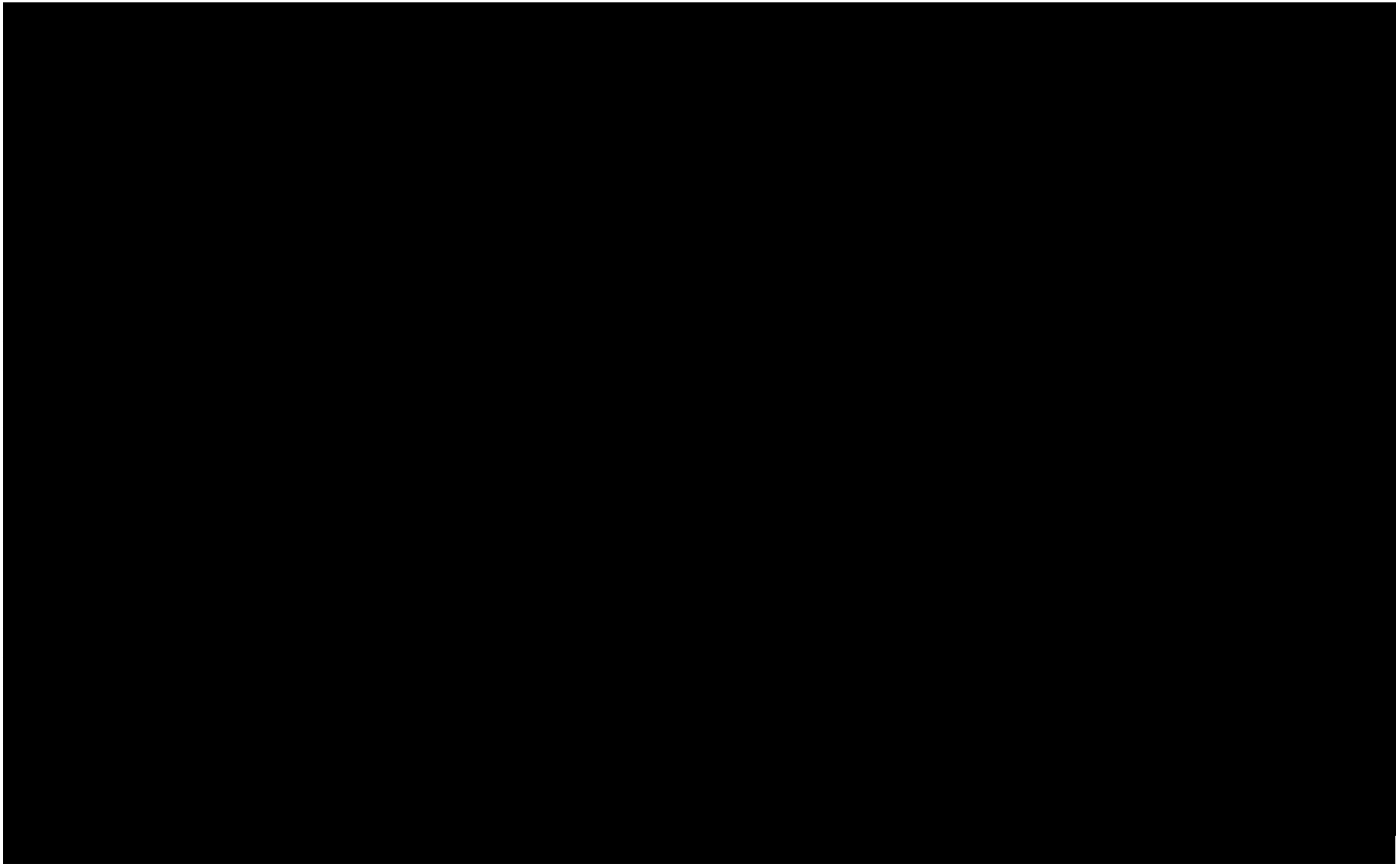
Abbreviations: ICER, incremental cost-effectiveness ratio, LYG, life year gained; QALY, quality-adjusted life year; SoC, standard-of-care.
łSoC is limited to maximally tolerated statins, other lipid lowering therapies excluding ezetimibe and no treatment.

Table 40: Results for primary prevention HeFH patients with LDL-C ≥5.0 mmol/L, statin intolerant

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC[ł]	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Inclisiran+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alirocumab+SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evolocumab+SoC	[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.
łSoC for the statin intolerant population includes ezetimibe, other lipid lowering therapies and no treatment.

Appendix



NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **9 March 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Dr Alan Jones**
2. Name of organisation	**University Hospitals Birmingham NHS FT**
3. Job title or position	**Consultant Physician**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it **x**☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation	☐ yes

submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of the treatment is to lower plasma LDL cholesterol concentrations in patients with, or at risk of developing, atherosclerotic cardiovascular disease (ASCVD) with the intention of reducing subsequent cardiovascular events. There is a well established evidence base for the clinical relationship between lowering LDL cholesterol., by whatever means, and the future chance of CVD events.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	The accepted view is that every 1.0 mmol/L reduction in LDL cholesterol translates into a 21% risk reduction in ASCVD. There are reasons to think that lowering plasma LDL cholesterol to < 2.6 mmo/L is a suitable target for treatment and that is difficult to achieve with currently available oral therapies, that is statins and ezetimibe.

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes for both. Lowering LDL cholesterol to below 2.6 mmol/L is difficult to achieve with oral therapies alone, and the eligibility criteria for PCSK9 monoclonal inhibitors, used either as an addition to statins, or as monotherapy in 'statin intolerant patients' preclude large number of patients from monoclonal therapy. So for example in a primary prevention context, patients with Type 2 diabetes mellitus, of whom two thirds will die from ASCVD, are currently ineligible for monoclonals, as are those with non Familial Hypercholesterolaemia. Approximately 20% of patients with an FH phenotype actually have monogenic FH, but the remainder with polygenic disease are also ineligible despite having a high ASCVD risk. For secondary prevention of ASCVD it is also difficult to lower LDL < 2.6 mmol/L with oral therapy, and the LDL eligibility levels for monoclonal inhibitors of 3.5 or 4.0 mmol/L also preclude therapy in a significant number of patients.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	With statins and or ezetimibe with the addition of twice monthly monoclonal PCSK9 inhibitors is patients fit the eligibility criteria.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CG 71 for FH, NICE CG181 for lipid modification, and the European Society of Cardiology and European Atherosclerosis for treatment of dyslipidaemias.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	I think the pathway of care for secondary prevention of ASCVD is well defined, in that patients are routinely prescribed a high intensity statin (Atorvastatin 80 mg od), possibly also Ezetimibe 10 mg od) , but are not commonly started on PCSK9 monoclonals. For primary prevention, general practice is well aware of FH and in the absence of a genetic hyperlipidaemia CVS risk assessment with QRISK is also the norm.

• What impact would the technology have on the current pathway of care?	It would be an addition to oral therapy, but a lower LDL eligibility threshold and a wider inclusivity for primary prevention would I think have a major impact on the numbers whose LDL cholesterol levels are satisfactorily treated. Because of the twice yearly dosing regime administered by a healthcare professional, it also obviates any issues of compliance,
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Essentially I think this technology will replace the use of monoclonal PCSK9 inhibitors, since it's twice yearly rather than twice monthly, and will extend the treatment option to a wider range of patients than can currently be treated.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The submission says primary care. I think however that GPs may be reluctant to consider this option for now, and it would be best to start off with it being a secondary care/specialist clinic initiated treatment with monitoring for at least one year before a shared care arrangement is put in place. Some patients do not respond to monoclonal PCSK9 inhibitors and it seems that some do not respond to Inclisiran either. There is also a wide range of responses to PCSK9 monoclonals as there are with Inclisiran seemingly, and as far as I am aware there is no way of predicting response.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This would require nursing time to administer two S/C injections a year. Nothing else would be required over and above that which is in place already.
13. Do you expect the technology to provide clinically meaningful	Yes

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes, by reducing ASCVD events, be they strokes, acute coronary syndromes or critical lower limb ischaemia.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, by reducing morbidity from strokes, acute coronary syndromes or lower limb amputations.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It should be as effective across patient subgroups, but it may well be very appropriate for those who are unable to tolerate conventional oral therapy.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	It appears to me to be easier for patients in that they would not have to self administer injections, and that it is two injections a year rather than 24. This would require some additional healthcare support to administer the drug. No additional testing would be needed.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There is a wide range of LDL responses to PCSK9 monoclonals as there are with Inclisiran, and I imagine that one would want to withdraw treatment with an inadequate LDL lowering response. One would wish tomeasure serum lipids anyway, so no additional testing..
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I don't think so.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. The major therapeutic advances in this area have been the statins in 1988, PCSK9 monoclonals in 2016, and now this one in 2021. I think however this is a 'game changer' in that it will allow a far wider and greater reduction in LDL levels than ever before with far more certainty that the drug is in the patient..
• Does the use of the technology address any particular unmet need of the patient population?	Yes in that we currently do not the treatment modalities to adequately lower LDL cholesterol in a substantial number of patients at high risk of future ASCVD events.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	It appears that the only significant side effect will be injection site reactions, which does not appear to have had any major impact on patient acceptance of the treatment.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK	The evidence base is on three RCTs, ORION 9, 10 and 11. No UK patients were enrolled in ORION 9 and 10, but I

setting?	really rather doubt that the RCT results would not be applicable to UK patients.
• What, in your view, are the most important outcomes, and were they measured in the trials?	These are relatively small scale short duration studies which were only powered to look at LDL reductions. The most important outcome will be the effect on ASCVD events and that will have to await the outcome of the ORION 4 study, which is being run in the UK and USA. I think the results will be delayed since UK research has been largely paused due to the COVID restrictions.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The surrogate for ASCVD events is LDL reductions, but there is overwhelming evidence that there is a strict proportionality between LDL lowering and ASCVD events, wherein a 1.0 mmol/L LDL reduction translates to a 21% reduction in ASCVD events
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	No

of NICE technology appraisal guidance [TA385, TA393, TA394]?	
23. How do data on real-world experience compare with the trial data?	Trial patients are always different to real world patients, but the cardiology view is that LDL lowering is of great benefit in the real world.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am ware of.
24b. Consider whether these issues are different from issues with current care and why.	N/A
Topic specific questions	
25. Does previous treatment with ezetimibe or another lipid lowering treatment affect	Not in terms of efficacy. Oral therapies may well lower LDLs to below the eligibility threshold, which is obviously desirable but not routinely achievable.

outcomes with inclisiran?	
26. Will inclisiran be given in addition to treatment with statins and/or ezetimibe?	It would be given in addition to statins/ezetimibe if LDL targets were not achieved, or as monotherapy if oral therapy is not tolerated or contra indicated.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Inclusion of ezetimibe as part of standard care rather than as an active comparator	I think ezetimibe would normally be considered as part of standard of care.
Additional issue 1: Generalisability of the results from the ORION-9 and ORION-10 studies	I think they would be generalizable.
Additional issue 2: lack of genetic testing results in some Familial hypercholesterolaemia	FH is a relatively common genetic disorder and the estimated prevalence is 1 in 250, suggesting 240,000 affected individuals in Britain. The condition is under diagnosed with the NHS Long Term Plan using a figure of just 7% of affected people being diagnosed with FH through genetic testing. Genetic testing for FH is now available from the GLHs and is on the NHSE inventory as the R134 panel. Experience

cases being missed	is that only 21% of those with an 'FH phenotype', actually have monogenic FH, with the majority of the rest having a polygenic disorder, with those with a high polygenic risk score having substantially elevated ASCVD risks.
Additional issue 3: lack of a scenario analysis using event rates from Beliard, 2018 because of technical errors in the company's economic model	I do not think I have the health economic experience to comment on this.
Additional issue 4: The impact of of differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations	HeFH and ASCVD patients are clearly not homogeneous groups in terms of their future CVD risks, but these risks are clearly substantial and I don't think anyone could rationally argue that not lowering LDL cholesterol effectively, and managing other CVD risk factors optimally, should be the standard of care. The efficacy outcomes from the ORION studies can only focus on LDL cholesterol changes as a surrogate for future ASCVD events. There is no evidence that increasing HDL cholesterol achieves any clinical benefit, and I don't think is relevant.
Are there any important issues that have been missed in ERG report?	I think defining 'adults in a primary prevention category with elevated risk (PPER), needs to be thought through. The paper talks about Framingham CVD risks of > 20%, but UK practice is to use QRISK and a calculated CVD risk of > 10% over 10 years for lipid lowering therapy. This would include most men in their 50s and most women in their 60s. Also there is a suggestion that elevated PPER patients and ASCVD patients with LDL cholesterols > 2.6 mmol/L on whatever or no therapy should go to Inclisiran, but also failing that go to secondary care for monoclonal PCSK9 inhibitor therapy. I cannot see that this makes any sense, and it's my guess that Inclisiran will largely if not

	completely replace PCSK9 monoclonals

PART 3 -Key messages

27. In up to 5 sentences, please summarise the key messages of your statement:

- This drug opens up the potential for far larger reductions in LDL cholesterol, in more patients, which should translate to future ASCVD reductions
- It is likely to be welcomed by patients due to the twice annual dosing regime.
- The eligibility criteria need to be less onerous than for the PCSK9 monoclonals, otherwise patients will just transition from monoclonals to Inclisiran and we won't be any further forward.
- I think this is likely to be a 'game changer' drug.
- There are no CVD outcome studies as yet, but it is entirely reasonable to assume that ORION 4 will show those, since if not this would be the only drug ever to reduce LDL cholesterol and not reduce ASCVD, and we already know that taking out PCSK9 with monoclonals (Fourier and Odyssey) achieves that.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

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Clinical expert statement & technical engagement response form

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

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  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	**Professor Kausik Kumar Ray**
2. Name of organisation	**Imperial College London**
3. Job title or position	**Professor of Public Health and Honorary Consultant Cardiologist/** Deputy Director of Imperial Clinical Trials Unit, NIRC ARC National Lead Cardiovascular Disease, Clinical Research Lead for HDR UK Digital Innovation Hub NW London (DISCOVER NOW), President of the European Atherosclerosis Society
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil/ Never**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to reduce long-term exposure to LDL Cholesterol (LDL-C) as a means to reduce the future risk of cardiovascular disease. As benefit is quantifiable with LDL-C reduction, the aim is to not over treat low risk individuals and not undertreat high risk individuals. Though the wording of this review to to treat hypercholesterolaemia, this is misleading. As CV risk is reduced by about 20-22% per 1mmol/L lowering, even a 0.5mmol/L lowering produces large absolute benefits in someone with very high absolute risk eg 10 risk of 50%. The absolute benefit could be greater than for instance a 2mmol/L lowering in someone with a modestly elevated LDL-C with a 10-year risk of 5%. Thus both LDL-C lowering in absolute terms (a function of potency and baseline LDL-C) as well as baseline risk should be considered.
9. What do you consider a clinically significant treatment	

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Global guidelines for lipid lowering have evolved to recommend lower risk based LDL-C. For instance in 2019 European Society of Cardiology/ European Atherosclerosis Society recommend both a 50% reduction in LDL-C and an LDL-C below 1.4mmol/L for those with established CVD and very risk primary prevention, for high risk primary prevention the recommended goals are < 1.8mmol/L. US (ACC/AHA 2018) guidelines are fairly similar recommending levels below 1.8mmol/L. UK guidance has not been updated since 2014. In 2016 using CPRD (Steen D, Ray et al BMJ open) mean LDL-C in secondary prevention patients was 2.3mmol/L and 2.4mmol/L for high risk primary prevention. Both on treatment levels. These numbers have not changed and if anything are marginally worse. The Da Vinci EU registry (Ray EJPC 2021)which included the UK showed that the majority of lipid lowering is monotherapy with statins (84%). This approach will result for instance in only 1 in 5 patients with cardiovascular disease reaching goal (<1.4). The use of ezetimbe would result in an additional 20-25% achieving goal (combo therapy) but this means about 5-60% will still not be at goal. Use of PCSK9 Mab are more effective and using these would help more patients get to goal, but the current LDL-C threshold is >4mmol/L for most so they are underutilised meaning the vast majority of UK patients are in “no man’s land”, not at goal and can’t get access to a Mab. Finally, small molecules statins and ezetimibe are at the mercy of patient adherence, which together with unsatisfactory use of intensive LDL-C lowering regimens accounts for about 24/ 1000 extra cases of CVD per year (Khunti KK, Ray KK JAMA Network Open 2019). Thus there is an unmet need
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Poorly. As NICE have not recommended LDL-C goals nor indeed non-HDL-C goals most primary care tend to use between 20mg-40mg atorvastatin or equivalent. Ezetemibe use in combination with statins is low (~7%) largely as NICE have not updated this since 2014. Statins and ezetimibe are generic and these should be used in combination as standard of care but aren’t. When patients have the good fortunate to interact with some secondary care and lipid clinics in the UK, most specialists would add in ezetimibe as standard of care for instance for those with CV disease. Ezetimibe in

	primary care in particular and for some secondary care is often only considered as monotherapy when there is statin intolerance.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Primary Care tend to follow NICE 2014. Secondary care realises these are out of date and follows ESC/EAS 2019
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is clear but outdated. In primary care statin only and achieve a 40% reduction in non-HDL-C. Primary care usually only refers to secondary care when someone is statin intolerant or in a few cases where they understand the concept of risk better and for instance refer someone for potential add on therapies when they consider the LDL-C to be too high. However, primary care often does not recognise an LDL-C that is say 2.6 as being high for someone with CVD and multiple comorbidities and might only refer if say the LDL-C were 4. In contrast secondary care uses higher intensity statins and ezetimibe more, however this does vary between secondary care sites with the premier tertiary academic units being much more aggressive than some DGHs, where often its statin and let the GP manage lipids, citing NICE 2014.
• What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This therapy would/ should be an add on therapy to maximally tolerated statins plus ezetimibe which should be the default standard of care. This technology should be added on top of this standard of care for patients who are inadequately controlled. One of the major drawbacks of the current pathway for MAbs resulting in poor uptake is that they are secondary care only, so there are a considerable number of PCSK9 MAb eligible patients sitting in primary care not being referred
• How does healthcare resource use differ between the technology and current care?	If this is provided at a reasonable price, the cost of the technology can be easily offset by the number of events prevented.
• In what clinical setting should the technology be	Primary care and secondary care

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Modest. This is a subcutaneous inejction and can be performed by a healthcare assistant, nurse, pharmacist in the community.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Absolutely. It provides additional LDL-C lowering of about 52%. If on average it were used in the patients with an average LDL-C of 2.6-3.0 mmol/L we would expect 10 year CVD risk to be reduced by around one third. Moreover its long duration of action overcomes some of the issues of non-adherence related to many polypharmacy approaches using small molecules. A 6 monthly regimen offers the NHS a chance to reinforce healthy behaviours and adherence to background treatments.
• Do you expect the technology to increase length of life more than current care?	Yes is started early enough. The main reason is the reduced variability in cholesterol means a better long-term area under the curve so this therapy mimics much more the scenario of people with genetically lower LDL-C levels where the benefit is greater than anticipated by the absolute change/ difference in LDL-C as levels are sustained and low levels consistently for longer
• Do you expect the technology to increase health-related quality of life more than current care?	Yes significantly see above
14. Are there any groups of people for whom the technology would be more or less effective	This would be more cost effective in ASCVD patients (secondary prevention), especially if comorbidities are present where absolute risks are higher. Also in HeFH patients with lifelong elevations in LDL-C it would be more cost effective.

(or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Given the administration of vaccines in primary care , the use of this technology is not difficult. There are no extraneous costs. This is subcut 1.5ml injection. The safety profile in the studies is excellent, so no waiting watching etc that is currently needed for the current COVID vaccines is even needed.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	LDL-C levels to initiate treatment. We haven't seen patients who do not respond. If the treatment is cheap then for instance the current threshold of 30% LDL-C lowering for PCSK9 MAbs which CCGs impose won't be a factor. In case of suboptimal response check the patient has not stopped the statins which can be addressed by communication and educating patients

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes fewer CVD events and cost effective
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. The editors of the NEJM where the ORION 10 and 11 trials were published in 2020, considered those trials to be among the 13 papers (trials) that were published in the NEJM that would transform medicine.
• Is the technology a 'step-change' in the management of the condition?	No therapy administered twice a year can maintain cholesterol levels as consistently and safely due to the highly specific novel mechanism of action. siRNA based technology are the future of non-communicable diseases and control of many lipid related risk factors.
• Does the use of the technology address any particular unmet need of the patient population?	Yes the need of additional LDL-C lowering, adherence to any ad on therapies.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minimally if at al. Very safe no lier, renal, platelet or any other toxicity issues. Small risk of injection site adverse events. So itching, redness, pain in 2-4%. Reduced with use of prefilled syringes. Did not occur with every injection and most did not get a recurrence.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. UK patients enrolled and it reflects UK management
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Time averaged LDL-C reduction (peak and trough effect) between days 90-540 which tells you what you are likely to see with twice yearly dosing from year two. Peak effect at Day 510. Safety over 540 days
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Suurogates were not used
• Are there any adverse effects that were not	No

apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No the pooled data from ORION 9, 10 , 11 has been published in 2021 Wright S Ray KK JACC
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA385, TA393, TA394]?	No
23. How do data on real-world experience compare with the trial data?	Not available in UK yet. It is being used in Europe. To date nothing adverse has come to light.
Equality	
24a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	
Topic specific questions	
25. Does previous treatment with ezetimibe or another lipid lowering treatment affect outcomes with inclisiran?	PCSK9 Mabs target the same pathway and were prohibited. Patients with or without ezetimibe get similar LDL-C lowering. Patients with or without statins get similar LDL-C lowering. Where there might be numerical differences eg in HeFH versus other conditions, remember that benefit is related to absolute LDL-C lowering so a 47% lowering from an LDL-C of 4 is a clinically meaningful reduction versus say a 52% lowering in someone with an LDL-C of 2.6 as risk is lowered by 22% per 1mmol/L lowering
26. Will inclisiran be given in addition to treatment with statins and/or ezetimibe?	Yes if LDL-C is above threshold NICE consisders cost effective. Some patients will not be on statins (intolerance) and so on eztemibe only. Most should be on statins and ezetimibe and only those with LDL-C that are unsatisfactory despite the two generic being used should be offered the drug.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Inclusion of ezetimibe as part of standard care rather than as an active comparator	Ezetimibe should be considered standard of care. See above comments
Additional issue 1: Generalisability of the results from the ORION-9 and ORION-10 studies	Yes these can be generalised to the UK
Additional issue 2: lack of genetic testing results in some	That's not relevant. The trails show that this therapy works across the board irrespective of mutation type. Genetic testing is freely avalable in most centres in secondary care. It is not in primary care. For patients in primary care currently these patients are refrred to secondary care for testing, so the path to Inclisiran for such patients woul most likely be from secondary care or a letter to the GP to start Inclisiran because

Familial hypercholesterolaemia cases being missed	the genetic tests have confirmed. The aim of the NHS is to detect 25% more FH cases this decade vs < 10% detected. The problem is not genetic testing but doctors measuring LDL-C early enough and considering a diagnosis of FH
Additional issue 3: lack of a scenario analysis using event rates from Beliard, 2018 because of technical errors in the company's economic model	Any analysis done is my opinion limited for 10 year risk estimation. Most models use crude univariate characteristics, rather than multiple characteristics that provide a more robust assessment of 10 year risk, which incorporates prevalence of all comorbidities. In part this is limited by the lack of use of appropriate secondary prevention risk calculators like SMART. These have been validated in CPRD and perform as well as the derivation cohorts. This any model is only as good as the assumptions f risk and distribution of comorbidities.
Additional issue 4: The impact of differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations	This is not an issue. LDL-C % reduction is constant. The percent reduction is modestly lower in HeFH but as explained above absolute reductions are greater as starting LDL-C is higher. Consistent benefit was observed across primary and secondary prevention. HeFH has a very high absolute risk so for instance in ESC guidelines HeFH with a single additional risk factor is considered as the same risk as ASCVD (LDL-goal (<1.4) and HeFH alone high risk LDL-C goal <1.8 is recommended. So broadly these would bethe groups that need this technology. HDL-C is not a factor no treatments have been shown that altering this impacts outcomes.
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

27. In up to 5 sentences, please summarise the key messages of your statement:

- The technology is a sea change in our ability to reduce cholesterol in high risk patients
- The technology is safe with no specific additional monitoring needed so ideal for primary care
- The technology is an add on to standard of care (which is maximally tolerated statins plus ezetimibe)
- The technology provides a way of improving population level control of LDL-C when administered by a healthcare professional, much like coverage of populations to lower levels of pollution
- This approach given the average 10 year risk and cholesterol levels currently achieved despite statins should reduce CV events by one third in relative terms

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Technical engagement response form

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm on 10 March 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**HEART UK- The Cholesterol Charity**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Inclusion of ezetimibe as part of standard care rather than as active comparator	**YES**	Ezetimibe is only effective if they are taken by patients on a regular basis, yet patients still do not have uniform access. There is a large variation in cholesterol management by GPs. For example, there is a 467% difference between uptake rates for ezetimibe in NHS Tower Hamlets CCG and NHS Stafford and Surrounds CCG. Inaccessible treatment options put patients at a greater risk of a number of heart diseases and disproportionately affects those from more deprived areas, with premature death rates from CVD in the most deprived 10% of the population almost twice as high as rates in the least deprived 10%. Many patients are reluctant to express doubts and concerns about medicines and frequently will stop taking medicine without exploring all additional alternatives. For example, 75% of people started on a statin discontinuing treatment within 2 years and will be at an increased risk of major CV events. Those at high CVD risk who report a potential intolerance to recommended high intensity statin treatment may be offered a lower dose statin, an alternative statin or be advised to stop taking statins for 4 – 6 weeks before ezetimibe. This pathway may not always be completed by many patients and will account for some of the variations in ezetimibe prescribing and patients discontinuing treatment.

		Inclisiran has the benefit as a twice yearly injection rather than a daily medication and patients should be offered it as an option in addition to ezetimibe to ensure they are receiving an effective lipid lowering therapy, rather than stopping medication as is currently the case too often or being treated sub-optimally.
Additional issue 1: Generalisability of the results from the ORION-9 and ORION-10 studies	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Additional issue 2: lack of genetic testing results in some Familial hypercholesterolaemia cases being missed	**YES/NO**	Should be consistent with NICE Clinical guideline [CG71] and the NHS Long Term Plan for England target of finding at least 25% of those with FH through the NHS genomics programme by 2024. It should however be noted that many patients are reluctant to get a genetic test due to the consequences on some employment and insurance.
Additional issue 3: lack of a scenario analysis using event rates from Beliard, 2018 because of technical errors in the company's economic model	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or
Additional issue 4: The impact of of differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes focused on		

changes in LDL-C, HDL-C, and discontinuations		

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Cardiovascular Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Inclusion of ezetimibe as part of standard care rather than as active comparator	**No**	It is appropriate to assume ezetimibe as part of standard care. It is a well tolerated, evidence-based and (as it is generic now) cheap treatment for hypercholesterolemia. BCS notes that, despite these strengths to ezetimibe, it is not always prescribed as widely as would be expected for a treatment with such benefits. Nevertheless, BCS feel that it should be considered part of standard treatment, as opposed to a comparator for inclisiran or any other newer lipid agent. We feel the comparison against ezetimibe, as opposed to seeing ezetimibe part of baseline care, would introduce an unnecessary step to uptake. We are concerned that this could unduly delay or restrict usage of this medication, especially as the management would be principally in primary care rather than in specialist lipid clinics.
Additional issue 1: Generalisability of the results from the ORION-9 and ORION-10 studies	**No**	The results of the ORION 10 and 11 trials are generalizable. They reflect populations managed in everyday care in the NHS. They also reflect the effect of inclisiran in high risk patients who despite current lipid lowering therapies do not achieve sufficiently low LDL-C levels for their level of risk and where additional therapies could be of benefit.
Additional issue 2: lack of genetic testing results in some Familial	**no**	This is realistically not an issue. Yes genetic testing is not available in primary care, however most if not all specialist lipid clinics in the UK have

hypercholesterolaemia cases being missed		access to genetic testing through the genomics England hubs. The issue is getting people with potential FH to lipid clinics. Efforts to check cholesterol and refer appropriately would help fix some of the issues about patients not being identified.
Additional issue 3: lack of a scenario analysis using event rates from Beliard, 2018 because of technical errors in the company's economic model	**No**	One of the issues with any economic model is it collapses data and produces an average. Patients with atherosclerotic cardiovascular disease (ASCVD) are a heterogeneous group with respect to event rate. That said CPRD data in patients with ASCVD routinely managed is England have a 10 year event rate of CV death non-fatal MI or stroke of about 26%. The average LDL-C in different risk cohorts can be obtained from (Steen D et al BMJ Open) and the impact of adherence and intensity of LDL-C lowering on outcomes from Khunti K et al JAMA Network Open.
Additional issue 4: The impact of of differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations		The relative efficacy of LDL-C lowering is unaffected by comorbid states. So % reduction is constant with and without additional features. AS risk reduction depends upon absolute reductions in LDL-C, the key determinant is baseline LDL-C which determines the relative risk reduction based on CTT. However, when this relative risk reduction is applied to calculate absolute benefits, then bigger ARR and smaller NNTs result with higher baseline risk due to comorbid states. Changes in HDL-C are irrelevant as to date no therapy has shown that raising HDL-C reduces cardiovascular events

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: general comment		No	BCS anticipate that inclisiran will prove highly cost-effective given the 50% reduction in LDL with only a twice yearly injection.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

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Professional organisation submission

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Thank you for agreeing to give us your organisation's views on inclisiran and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Primary Care Cardiovascular Society**

3. Job title or position	**Council Member**
4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The PCCS is a multidisciplinary organisation reflecting the ideas and opinions of primary care teams involved in the management of cardiovascular disease throughout the UK.** **We are an independent organisation run by volunteer healthcare professionals with a passion for high-quality cardiovascular care and a clear belief in editorial independence. We are supported by a professional secretariat. We have received funding through membership subscription (although this is currently free) and through partnerships with other organisations including pharmaceutical companies.**
4b. Has the organisation received any funding from the manufacturer(s) of inclisiran and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**Yes.** The PCCS has received funding from Novartis as follows: - £10,000 as part of our industry partnership programme - £6580 to support our series of Primary Care Heart Failure Webinars - £9000 to support our 2020 Annual Conference

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for primary hypercholesterolaemia or mixed dyslipidaemia	
6. What is the main aim of treatment? (For example, to reduce LDL cholesterol, to cure the condition, or prevent progression or disability.)	To reduce CV mortality & morbidity
7. What do you consider a clinically significant treatment response? (For example, a reduction in LDL cholesterol by a certain amount.)	We recognise that a 1mmol/l reduction in LDL has been demonstrated to reduce major cardiovascular events but we believe that we should be aiming for a more substantial reduction in LDL level and we would argue that the NICE target (whether it is the current individualised target or a future NICE approved target)

8. In your view, is there an unmet need for patients and healthcare professionals in primary hypercholesterolaemia or mixed dyslipidaemia?	Yes.
What is the expected place of inclisiran in current practice?	
9. How is primary hypercholesterolaemia or mixed dyslipidaemia currently treated in the NHS?	For most people, these are managed with a combination of lifestyle advice and statins (with ezetimibe less often used either as an add-on or instead of statins). Some people are seen in specialist lipid clinics but this is a smaller group and feedback from our members indicate that waiting times for specialist lipid clinics have been increasing (even prior to the Covid-19 pandemic) We believe that there is further room to improve cardiovascular risk reduction through effective implementation of lipid lowering strategies.
• Are any clinical guidelines used in the treatment of primary hypercholesterolaemia or mixed dyslipidaemia, and if so, which?	NICE guidelines and local/regional guidelines (usually based on NICE) exist but the feedback we receive suggests that these guidelines are often misunderstood and that people are frequently under-treated (with one example being that many clinicians think “fire and forget” is still part of the NICE guideline. WE believe that QOF improved the implementation of cardiovascular risk reduction strategies but the change in emphasis within QOF appears to have contributed to a reduced emphasis on proactive risk reduction.
• Is the pathway of care well defined? Does it vary or are there	The pathway is well defined but poorly understood and we believe poorly applied. The feedback from our members suggests that there is significant variability in application.

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would inclisiran have on the current pathway of care?	We believe that inclisiran would allow us to help a greater percentage of patients reach appropriate lipid targets. The data suggest that lipid-lowering reduces cardiovascular mortality and morbidity and although we await inclisiran mortality data, we expect that the “lower is better” phenomenon is likely to be reproduced. A clear and simple guideline with clear targets will beneficial. It will be important to avoid confusion by having inclusion criteria and targets measured using either LDL or non_HDL (not having one used in one lipid guideline and another used elsewhere)
10. Will inclisiran be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – we believe that Inclisiran will be possible to use safely and effectively in primary care (where most of the relevant patients are already managed). Lipid clinics are already over-burdened and this drug needs to be initiated within primary care in order to fulfil its potential.
• How does healthcare resource use differ between inclisiran and current care?	The primary care team is the healthcare resource used to manage most lipid problems. We believe that primary care is ideally placed to find, assess and manage the most appropriate patients for this medication. Primary care is used to injectable agents and is well set-up to deliver this medication. There is the potential for a better use of resources with a twice-yearly injection, fewre repeat prescriptions and fewer dispensing encounters.

	There will be a need for education in the roll-out phase of this drug for both primary and secondary care colleagues.
• In what clinical setting should inclisiran be used? (For example, primary or secondary care, specialist clinics.)	We believe that primary care is the best setting for this drug as it is where the patients are and its is where most lipd treatment is currently provided. This drug will be beneficial for target attainment within the anticipated primary care DES.
• What investment is needed to introduce inclisiran? (For example, for facilities, equipment, or training.)	The main investment will be in education relating to lipid targets and the new medication itself. Primary care already has the patient population, disease registers, call/recall capabilities and the expertise to administer and monitor the medication.
11. Do you expect inclisiran to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect inclisiran to increase length of life more than current care?	Yes. We recognise that mortality data is awaited but based on what we currently understand regarding lipids, we anticipate a mortality benefit.
• Do you expect inclisiran to increase health-related quality of life more than current care?	Yes.

12. Are there any groups of people for whom inclisiran would be more or less effective (or appropriate) than the general population?	We anticipate that the patients with the highest cardiovascular risk will benefit more. Primary care is therefore ideally placed to identify such patients.
The use of inclisiran	
13. Will inclisiran be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Primary care is skilled at identifying high risk patients, arranging recall and monitoring outcomes. Primary care teams already have the expertise to administer injectables. While some patients will be fine with current treatments, other struggle with tolerability and many are unale to reach target lipid levels on current medications. Recall for injectable agents is already standard in primary care. No specific extra monitoring that would significantly impact on primary care workload.

14. Will any rules (informal or formal) be used to start or stop treatment with inclisiran? Do these include any additional testing?	NICE guidelines/appraisal will inform initiation and monitoring guidelines
15. Do you consider that the use of inclisiran will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. Reduction of cardiovascular mortality and major adverse cardiovascular events.
16. Do you consider inclisiran to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Current oral lipid-lowering medications are variably tolerated. Compliance is the achilles heel of lipid management and this new medication provides us with a valuable additional tool with which to protect our patients.

• Is inclisiran a 'step-change' in the management of primary hypercholesterolaemia or mixed dyslipidaemia?	Yes
• Does the use of inclisiran address any particular unmet need of the patient population?	Yes – this can help us manage CV risk more effectively especially in high-risk patients and those who are unable to tolerate conventional therapy. The new medication can also help us address the significant residual risk that exists even in well treated patients who have established cardiovascular disease
17. How do any side effects or adverse effects of inclisiran affect the management of primary hypercholesterolaemia or mixed dyslipidaemia and the patient's quality of life?	The trial data suggest that this is a well-tolerated medication.
Sources of evidence	
18. Do the clinical trials on inclisiran reflect current UK clinical practice?	Yes. The trials address the kind of patients that we see in everyday clinical practice.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Mortality reduction s the most important outcome but we recognise that all evidence-based lipid-lowering agents need to begin their trial programme with studies that show a significant lipid-lowering effect while maintaining safety.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA385, TA393 and TA394?	No
21. How do data on real-world experience compare with the trial data?	We believe that there is nothing at this time to suspect that real-life experience will be significantly different to the trial data
Equality	
22a. Are there any potential equality issues that should be taken into account when considering inclisiran?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messagesN/A
23. In up to 5 bullet points, please summarise the key messages of your submission. • There is an unmet need in treatment especially for high-risk patients • The data suggest that inclisiran is safe and effective • Primary care is ideally positioned to identify, risk-stratify, treat and monitor patients with this new medication • Guidelines need to be clear, concise and avoid the use of multiple threshold variables • This new medication offers a significant opportunity to reduce residual cardiovascular risk

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Technical engagement response form

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm on 10 March 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Amgen Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Inclusion of ezetimibe as part of standard care rather than as active comparator	**NO**	-
Additional issue 1: Generalisability of the results from the ORION-9 and ORION-10 studies	**NO**	Results from ORION-10 (and also ORION-11) cannot be considered generalisable to patients with a recent atherosclerotic cardiovascular disease (ASCVD) event, since the studies excluded patients with a major cardiovascular (CV) event within 3 months prior to randomisation. Given these patients are at an increased risk of subsequent ASCVD (see Additional Issue 4), they require therapies providing rapid low density lipoprotein-cholesterol (LDL-C) lowering. Including these patients in the ASCVD base case when estimating risks from the Clinical Practice Research Datalink (CPRD) may overestimate the efficacy of inclisiran.
Additional issue 2: lack of genetic testing results in some Familial hypercholesterolaemia cases being missed	**NO**	-

Additional issue 3: lack of a scenario analysis using event rates from Beliard, 2018 because of technical errors in the company's economic model	**NO**	The Committee should fully explore uncertainty relating to event rates as discussed further under Additional Issue 5 below.
Additional issue 4: The impact of of differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations	**NO**	-

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Overview of additional issues identified	**See detail below**	**NO**	Key issues we believe require further exploration include: • the potential [redacted] of inclisiran efficacy in the company network meta-analysis (NMA) • the positioning of inclisiran ahead of proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (ie, evolocumab and alirocumab), despite less favourable efficacy and a less robust clinical evidence package • the assumption that inclisiran is initiated solely in the primary care setting • inconsistency in modelling approach vs that used in the appraisals of PCSK9 monoclonal antibodies • uncertainty arising from limitations in the clinical evidence package for inclisiran, and • appropriateness of model input parameters such as cardiovascular (CV) event rates and non-CV mortality. Taken together, these issues have the potential to significantly impact the outcome of this appraisal and are discussed further below.

Additional issue 1:

Potential [redacted]x of inclisiran efficacy in company base case NMA

Section 2.2.5.1 (Table 6)

Section 2.4 (Table 14)

Section 3.3.9 (Table 31)

Section 4.3 (Table 47)

NO

The company base case NMA estimates for inclisiran efficacy (ERG report Table 14) are more favourable than the co-primary endpoint results observed in the relevant clinical trials, and are potentially [redacted].

The company base case NMA estimates a [redacted]% reduction in LDL-C for inclisiran vs placebo for the ASCVD maximally tolerated dose (MTD) population (ERG report Table 14). This is based on estimated reductions in the NMA base case model of [redacted]% from ORION-10 and [redacted]% from ORION-11, both of which are substantially [redacted] than the co-primary endpoint results for these trials (see Table below). Similarly, the heterozygous familial hypercholesterolaemia (HeFH) MTD base case NMA estimates a [redacted]% reduction in LDL-C which is [redacted] than the co-primary endpoint results from ORION-9 (see Table below).

Comparison of inclisiran % LDL-C change vs placebo in trial primary endpoint analyses and the ASCVD MTD and HeFH MTD NMA base case models

	Published trial primary endpoint analyses *(Raal et al, 2020; Ray et al, 2020b)*		NMA base case model (% LDL-C change at [redacted])
	% LDL-C change at Day 510	Time-adjusted % LDL-C change (Day 90-540)	
ORION-10	-52.3%[a]	-53.8%	[redacted]%[b]
ORION-11	-49.9%[a]	-49.2%	[redacted] %[b]
Pooled ORION-10 and ORION-11	[redacted] %[a]	[redacted]%	[redacted]%[b]
ORION-9	-47.9%[a]	-44.3%	[redacted]%[c]

[a] Multiple imputation washout model (prespecified primary analysis methodology)
[b] Estimates for ASCVD MTD base case analysis
[c] Estimate for HeFH MTD base case analysis
Source: ERG report Tables 6 and 14; Company Submission Table 38, Table 39 and Figure 31.

Although we are aware that the NMA is conducted at a different timepoint to the trial primary analyses, it is surprising that the NMA LDL-C reductions are [redacted] and this generates uncertainty around the most plausible estimate of

			inclisiran efficacy. It is not clear what statistical model was used to generate the ORION-10 and ORION-11 NMA efficacy estimates for the ASCVD MTD population, but the company's pooled analyses of the 2 studies at [redacted] show that estimates are [redacted] the method of analysis used, with [redacted] results seen using an 'observed values' approach ([redacted]%) compared with the prespecified primary analysis multiple imputation washout approach ([redacted]%) (Company Submission Table 38). Importantly, this suggests that efficacy estimates are [redacted], which then calls into question the robustness of the base case NMA estimates. Another important factor likely to influence results in favour of inclisiran is use of the [redacted] timepoint for the base case NMA. As noted in the inclisiran Summary of Product Characteristics (SmPC), maximal LDL-C reduction in the phase 3 pooled analysis of ORION-9, ORION-10 and ORION-11 was achieved at Day 150 (based on follow-up of 540 days) *(Leqvio SmPC, 2021)*. Data from the ORION-1 study with inclisiran 300 mg dosing at Day 1 and Day 90 similarly show that the largest % reduction in LDL-C over the 240 day follow-up is seen at Day 150 *(Ray et al, 2017)*. The choice of timepoint for assessing LDL-C reduction is particularly influential for inclisiran compared with other therapies included in the NMA given the longer dosing interval and the profile of LDL-C change over time. Consequently, we consider the time-adjusted % change in LDL-C (Day 90-540), which is explored by the company in a scenario analysis, to be a more representative measure of inclisiran efficacy. This measure is not influenced by time since last dose and better reflects average inclisiran efficacy. Notably, inclisiran LDL-C reductions for the ASCVD MTD population using the time-adjusted measure ([redacted]x%) are [redacted] with the ORION-10 and ORION-11 primary endpoint results (see Table above) and also with the recently published Toth 2020 NMA identified by the ERG (50.17%) *(Toth et al, 2020)*. **We strongly recommend that NICE fully explore the impact of the above issues and ensure that the base case model does not [redacted] the efficacy of inclisiran.** In light of these comments, the company's conclusion from their NMA that inclisiran outcomes are 'expected to be comparable to alirocumab and evolocumab' (Company Submission section B.2.9.4) does not seem reasonable and is likely a consequence of [redacted] assumptions used for the base case NMA regarding inclisiran efficacy. Their conclusion of comparability is also

			inconsistent with the Toth 2020 NMA, which showed efficacy of PCSK9 monoclonal antibodies (evolocumab 140 mg Q2W/420 mg QM and alirocumab 150 mg Q2W) to be superior to that of inclisiran (with efficacy of inclisiran based on the published prespecified trial primary endpoint analyses using the more representative time-adjusted % LDL-C measure) *(Toth et al, 2020)*. The company scenario analysis assuming that PCSK9 monoclonal antibodies have the same efficacy as inclisiran (scenario analysis 1 in Table 47 of ERG report) is therefore implausible and should not be considered relevant for decision-making.

Additional issue 2: **Place of inclisiran in the treatment pathway and setting of care**	**Section 1.4 (Table 2)** **Section 2.2.5.5** **Section 3.3.13.1**	**NO**	**The proposed positioning of inclisiran in patients who are clinically eligible for PCSK9 monoclonal antibodies under existing NICE guidance risks patients receiving suboptimal treatment**. Patients at elevated risk should be treated with the most efficacious therapy to optimise outcomes in clinical practice, and available evidence suggests PCSK9 monoclonal antibodies to be more efficacious than inclisiran at lowering LDL-C levels (see Additional Issue 1 above). Furthermore, PCSK9 monoclonal antibodies have a more robust clinical evidence package with proven impact on CV outcomes, data supporting real-world efficacy and a large body of safety evidence *(Ray et al, 2020a; Sabatine et al, 2017; Schwartz et al, 2018)*. Positioning inclisiran ahead of PCSK9 monoclonal antibodies in the treatment pathway risks LDL-C levels not being optimally controlled and, **importantly, could prevent patients at elevated risk from being able to access PCSK9 monoclonal antibody treatment under current NICE guidance.** This is of additional concern given the longer timeframe to achieve maximal LDL-C reduction for inclisiran compared with PCSK9 monoclonal antibodies, which is particularly relevant for patients in need of rapid LDL-C lowering such as those with a recent ASCVD event (see Additional Issue 4 below). **It is important that NICE take these considerations into account when developing guidance.** **The assumption that inclisiran is initiated solely in primary care does not reflect established precedent with PCSK9 monoclonal antibodies and is inconsistent with NICE Clinical Guideline 181** which advises seeking specialist advice (including referral) for patients at an elevated risk of CVD and those with CVD who are intolerant to 3 different statins. The practical feasibility of initiating inclisiran in primary care should be clearly demonstrated given the challenges in identifying appropriate patients in this care setting, as well as the system/process burden that could be imposed on general practitioners given the need for a bi-annual recall and the inability to self-administer. We consider it unlikely that patients at elevated risk would routinely initiate inclisiran in the primary care setting and the appropriateness of this assumption should be explored further together with the impact on resource use in the model. We also question the company's suggestion that the majority of patients receiving evolocumab remain in secondary care in order to receive the patient access scheme price (ERG report section 3.3.13.1). After training for the first evolocumab injection, patients can self-inject or have homecare delivered to be managed in the

			community setting. This administration model is less burdensome to the patient and the National Health Service than that required for inclisiran dosing. Finally, it is important to note that all patients with elevated risk should benefit from access to PCSK9 inhibitors, regardless of care setting, to ensure optimal management of CV risk.
Additional issue 3: **Inconsistency of baseline LDL-C modelling approach vs the evolocumab and alirocumab NICE appraisals.**	**Section 3.3.4 (Table 24)**	**NO**	**The company's implementation of baseline LDL-C levels in the economic model is inconsistent with NICE's request for evolocumab and alirocumab assessment to evaluate cost effectiveness at the threshold LDL-C of the target population. This has the potential to significantly impact the conclusions of this appraisal.** For clarity and consistency with previous assessments, and in order to understand the cost effectiveness of inclisiran in all patients included in the target population, cost effectiveness should be evaluated at the LDL-C threshold of the population, and not at the mean LDL-C above that threshold. • Implementation of LDL-C thresholds in the company's economic model is based on mean LDL-C levels for patients above specific LDL-C thresholds (2.6 mmol/L threshold in base case analysis and 3.5/4.0/5.0 mmol/L thresholds in subgroup analyses by severity of hypercholesterolaemia). For example, a mean baseline LDL-C level of 3.47 mmol/L is adopted for the base case ASCVD population with LDL-C above the 2.6 mmol/L threshold) (ERG report Table 24). • However, no analyses have been provided by the company for LDL-C levels at the actual thresholds, which is in contrast to the analyses that were required by NICE in the appraisal of evolocumab (TA394) and alirocumab (TA393). Such analyses would ensure every patient above a certain LDL-C level is cost effective, rather than having patients at higher LDL-C levels subsidise patients at lower LDL-C levels. We believe NICE should employ consistency across appraisals and that appropriate LDL-C threshold values should be thoroughly explored to determine the impact on the estimated cost effectiveness of inclisiran.

Additional issue 4: **Limitations of inclisiran clinical evidence package**	**Section 3.3.10** **Section 3.3.15 (Table 40)**	**NO**	**Unlike PSCK9 monoclonal antibodies, the clinical evidence package for inclisiran lacks clinical outcomes data, long-term follow-up data and data on real-world use. This leads to uncertainty around longer term efficacy/safety as well as treatment discontinuation rates. In particular, the base case assumptions of an immediate and sustained treatment effect for inclisiran appear optimistic.** As noted by the ERG, there is a lack of evidence to support inclisiran treatment efficacy being maintained over the model time horizon (ERG report Table 40). While efficacy data for inclisiran is available for only up to 18 months, evolocumab has trial data showing a sustained treatment effect over up to 5 years *(Koren et al, 2019)* as well as real-world data supporting a sustained treatment effect in routine clinical practice *(Ray et al, 2020a)*. Although inclisiran has a similar mechanism of action to PCSK9 monoclonal antibodies, it is not identical and it cannot be assumed that inclisiran treatment efficacy will be similarly maintained over the longer term without evidence to support this. An analysis exploring the impact of inclisiran treatment waning is therefore relevant to decision-making (the ERG note that the company did not provide this [ERG Report Table 40]). The base case assumption of an immediate treatment effect for inclisiran is also questionable. Data from the ORION-1 trial show that the % LDL-C reduction after the first 300 mg inclisiran dose is less than 40% at D14 and that maximal treatment effect for a 2-dose regimen (Day 1 and Day 90) is not realised until Day 150 *(Ray et al, 2017)*. Similarly, Day 150 is the timepoint of maximal % LDL-C reduction over the 540-day follow-up in ORION-9, ORION-10 and ORION-11 (pooled phase 3 study analysis) *(Leqvio SmPC, 2021)*. This suggests that the base case analysis (immediate treatment effect) and the scenario analysis where the full impact of inclisiran is assumed to occur from Day 90 onwards are both optimistic. In contrast, maximal LDL-C reduction for evolocumab (140 mg Q2W or 420 mg QM) is generally achieved within 1 to 2 weeks after dosing *(Repatha SmPC, 2021)*. **This differential time to maximal LDL-C reduction for inclisiran vs PCSK9 monoclonal antibodies should be explored in the model and is relevant to considerations around the positioning of inclisiran in the clinical pathway.** Speed of LDL-C reduction is particularly important for patients with a recent ASCVD event who are at significantly higher risk of subsequent events during the initial months post-event *(Smolina et al, 2012; Stahmeyer et al, 2019)*. Early and intensive LDL-C lowering has been shown to reduce the risk of

			subsequent CV events in these patients *(Cannon et al, 2004; Navarese et al, 2014)*. The slower onset of action with inclisiran vs PCSK9 monoclonal antibodies is therefore a relevant consideration regarding optimal therapy for this patient group and we note that evolocumab has demonstrated rapid LDL-C reduction in patients with acute coronary syndrome when administered within 24 to 72 hours *(Koskinas et al, 2019; Leucker et al, 2020)*. In addition, there is a lack of evidence on inclisiran efficacy in patients with a recent ASCVD event (within 3 months) since they were excluded from the ORION-10 and ORION-11 trials. **We recommend that NICE take these considerations into account to ensure patients who are in need of rapid LDL-lowering to reduce their CV risk are able to receive optimal therapy.** The lack of longer term or real-world data on inclisiran persistence also leads to uncertainty around modelled discontinuation rates. In contrast, the evolocumab dosing schedule has been shown to be easily managed in clinical practice with a low rate of discontinuation *(Ray et al, 2018)*. Furthermore, while population-specific discontinuation rates have been applied for inclisiran in a scenario analysis (3.2% per year for ASCVD and Primary Prevention Equivalent Risk [PPER], 1.7% for HeFH, Company Submission Table 71), a single discontinuation rate has been assumed for evolocumab and alirocumab regardless of population (based on data from their clinical outcomes trials in the ASCVD population). This likely favours inclisiran since lower discontinuation rates would be expected in the HeFH population (eg, real-world European data show a 1.4% discontinuation rate for evolocumab in the HeFH population over 12 months *(Ray et al, 2019)*). Finally, the company suggestion that the inclisiran administration schedule may lead to improved adherence compared with PCSK9 monoclonal antibodies is untested with no real-world data to support it, and does not reflect the convenience aspect of self-administration at home for PCSK9 monoclonal antibodies. Potential adherence issues for inclisiran (eg, resulting from delays to planned 6-monthly appointments) may have a greater impact on LDL-C control compared with PCSK9 monoclonal antibodies given the longer dosing schedule and slower time to full treatment effect (Inclisiran EPAR Figure 3.3.2.12) *(Leqvio EPAR, 2020)*.

<table>
<tr>
<td>Additional issue 5:

Appropriateness of baseline CV event rates</td>
<td>Section 4.1 (Tables 41, 42 and 43)</td>
<td>NO</td>
<td>The incremental quality-adjusted life years (QALYs) for inclisiran vs Standard of Care (SOC) in the base case ASCVD population ([redacted], Table 41 ERG report) appear to be [redacted] when compared with those for evolocumab and alirocumab vs SOC in their respective NICE appraisals (0.40 to 0.45) (see Table below). This difference could be attributed to higher baseline CV rates, lower non-CV mortality, higher utility values, or a combination of these factors. The difference is likely driven by baseline CV event rates, although this is difficult to assess given the available data (Company Submission Appendix L not made available).

Comparison of incremental QALYs vs SOC for inclisiran and PCSK9 monoclonal antibodies in ASCVD population
<table>
<tr><th></th><th>Incremental QALYs vs SOC</th></tr>
<tr><td>Inclisiran company base case model (Table 41 ERG report). (Assessed for population with mean LDL-C = 3.5 mmol/L)</td><td>[redacted]</td></tr>
<tr><td>Evolocumab TA394 NICE revised model (NICE TA394, 2015) (Assessed at threshold LDL-C of 3.5 mmol/L)</td><td>0.40</td></tr>
<tr><td>Alirocumab TA393 NICE revised model (NICE TA393, 2016). (Assessed at threshold LDL-C of 3.5 mmol/L)</td><td>0.45</td></tr>
</table>
In addition, the difference in incremental QALYs for inclisiran vs SOC in the PPER population ([redacted]) compared with the PP (Primary Prevention) HeFH population ([redacted]) in the base case analyses suggests a [redacted] CV risk for non-HeFH patients in the PPER population, which seems counterintuitive.

It is difficult to assess the appropriateness of baseline CV event rates used for the ASCVD and PPER populations based on the data available (Company Submission Appendix L not made available) and we recommend that NICE explore this further.</td>
</tr>
</table>

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Summary of changes to the company's cost-effectiveness estimate(s)

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..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

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Technical engagement response form

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

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We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm on 10 March 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Daiichi Sankyo UK Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Inclusion of ezetimibe as part of standard care rather than as active comparator	**NO**	Daiichi Sankyo agrees with the ERG that ezetimibe should be included as an active comparator in this appraisal. Ezetimibe (with or without statins) is identified as a comparator for this appraisal in the NICE final scope document.[1] Specifically, ezetimibe was identified as a comparator in the following populations: • When statins are contraindicated or not tolerated • When statins are contraindicated or not tolerated, and ezetimibe does not appropriately control LDL-C, and evolocumab and alirocumab are not appropriate Ezetimibe with a statin was identified as a comparator in the following populations: • When maximally tolerated statin dose does not appropriately control LDL-C: • When maximally tolerated statin dose with ezetimibe does not appropriately control LDL-C and evolocumab and alirocumab are not appropriate) Therefore, the omission of ezetimibe as an active comparator does not satisfy the decision problem as set out by NICE. Further, it is stated in the ERG report that a NICE submission advisory board was convened in July 2020, where clinical and economic experts were clear in their feedback that ezetimibe should be included as an active comparator, rather than standard of care.[2]

		Ezetimibe is recommended by NICE (TA385)[3] in the following circumstances: • Ezetimibe is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated and as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who cannot tolerate statin therapy. • Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who have started statin therapy when: serum total or low-density lipoprotein cholesterol concentration is not appropriately controlled, either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy, and a change from initial statin therapy to an alternative statin is being considered. Since this NICE Technology Appraisal 385, a generic version of ezetimibe has become available with a lower acquisition cost to the NHS improving it's cost effectiveness and reducing the impact on NHS budgets compared with the branded medicine. Ezetimibe treatment is an established treatment in the lipid-lowering pathway, has cardiovascular outcomes data and is included in published treatment pathways and guidelines including the NICE Clinical Guideline 181,[4] the National Guidance for Lipid Management for Primary and Secondary Prevention of cardiovascular disease,[5] NHS England Statin Intolerance Pathway,[6] and the Academic Health Science Network Lipid Management and Familial Hypercholesterolaemia programme.[7] Ezetimibe use is increasing over time in the United Kingdom, and recent prescription data (March 2021) suggest that ezetimibe is being used by approximately 250,000 patients in the United Kingdom.[8] According to the positioning for inclisiran (as stated on page 127 of the ERG

		report), inclisiran could be used either with statin with or without other lipid-lowering therapy, or alone with or without other lipid-lowering therapy. This positioning includes patients without prior or background ezetimibe treatment (without other lipid-lowering therapy). In these populations, active ezetimibe should be considered a comparator as it is recommended by NICE following Technology Appraisal, specified in the Final Scope and included in clinical guidelines. Daiichi Sankyo would like to highlight that ezetimibe background therapy was received by substantial proportions of patients in the ORION studies (25%-26% in ORION 1, 50%-56% in ORION 9, 10% in ORION 10, and 6%-7% in ORION 11),[2] suggesting relatively high uptake of ezetimibe in patients eligible for inclisiran.
Additional issue 1: Generalisability of the results from the ORION-9 and ORION-10 studies	**YES/NO**	As noted in a recent review performed by the Institute for Clinical and Economic Review, the inclisiran trials did not include many patients with statin intolerance, so the Institute were unable to determine if there may be differential effects of treatment or on safety events in this population.[9] Only 5.3%-10.8% of patients in the ORION trials were not on statins at baseline and were assumed to be statin intolerant. Daiichi Sankyo consider the evidence base to make a recommendation in this population is weak.
Additional issue 2: lack of genetic testing results in some Familial hypercholesterolaemia cases being missed	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Additional issue 3: lack of a scenario analysis using event rates from Beliard, 2018 because of technical errors in the company's economic model	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or
Additional issue 4: The impact of differences in CV risk and severity		There were statistically significant differences between subgroups for baseline LDL-C levels in the population with atherosclerotic cardiovascular disease. This

of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations		should be taken into account in the cost-effectiveness analysis as is a key driver in the model.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g., at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: **Baseline LDL-C**	3.3.4	NO	Table 24 in the ERG report presents the baseline characteristics of each modelled population, including mean baseline LDL-C which was estimated from the ORION trials. Daiichi Sankyo believes that these mean baseline LDL-C levels used by the company are not appropriate for the comparisons made in the cost-effectiveness analyses. In particular, comparisons of cost-effectiveness with PCSK9 inhibitors should reflect the population of patients who are eligible for PCSK9 inhibitors. Patients with cardiovascular disease are eligible for a PCSK9 inhibitor if their LDL-C concentration is persistently above 3.5 mmol/litre (for patients at very high risk of cardiovascular disease) and if LDL-C concentration is persistently above 4.0 mmol/litre (for patients at high risk of cardiovascular disease).[10] [redacted] Therefore,

			the mean baseline LDL-C of 3.47 mmol/litre for patients in the secondary prevention population appears to be low to inform the comparison between inclisiran and PCSK9 inhibitor comparators. Additionally, comparisons with active ezetimibe and no additional treatment should reflect the wider population of patients not eligible for PCSK9 inhibitors. This population will have a lower mean baseline LDL-C (and also are less likely to have pre-existing cardiovascular disease). [redacted]. Therefore, the mean baseline LDL-C assumed by Novartis appears to be too high to inform the comparison between inclisiran and ezetimibe or no further treatment. Baseline LDL-C (as well as other baseline characteristics affecting cardiovascular risk estimation) are significant drivers of cost-effectiveness.
Additional issue 2: **Heterogeneity in the NMA**	2.5.3	NO	The I2 value reported in the ERG report for the Company network meta-analysis used in the primary cost-effectiveness analyses was > 80%, indicating substantial heterogeneity.[2] [redacted]

			[redacted] It is not clear whether the submitting company has made all possible efforts to reduce the level of heterogeneity present in their analysis and this results in further uncertainty for decision-making. Additionally, for consistency with previous technology appraisals in this indication, the submitting company should be required to provide an additional network meta-analysis restricted to data from patients who have received prior ezetimibe to satisfy populations in the NICE scope where ezetimibe does not appropriately control LDL-C. It does not appear this has been presented in the company submission.
Additional issue 3: **Management of inclisiran in primary care**	NA	NO	From a clinical perspective, it is important to clarify how inclisiran treatment could practically be managed in a primary care setting, in view of the route of administration, dosing schedule, long half-life, and uncertainty with regard to long-term safety. Clinical feedback received by Daiichi Sankyo cites concerns around whether general practitioners in primary care would feel comfortable with delivering inclisiran without significant additional training and cause capacity issues which could impact on the delivery of

			other services. Input from clinicians on this issue would be valuable.
Additional issue 4: **No cardiovascular outcomes studies are ongoing in primary prevention patients**	2.2.2	NO	The main trial assessing cardiovascular outcomes with inclisiran (ORION-4, expected to read-out in 2024) includes only secondary prevention patients. This is not fully representative of the intended population in clinical practice of inclisiran. No cardiovascular outcomes data for primary prevention patients are anticipated; therefore, data verifying the efficacy of inclisiran in this population may not be available.
Additional issue 5: Commercial deal with NHS England	NA	NO	Daiichi Sankyo would like to seek assurances from NICE that the commercial arrangement that has been agreed between Med Co./Novartis and NHS England will not supersede the NICE process. In the interest of procedural fairness, consistency and transparency, it is important that any recommendation from NICE for inclisiran is evidence-based and follows a thorough assessment of clinical and cost-effectiveness against the relevant comparators as defined in the final scope for this appraisal. We are significantly concerned that a public announcement relating to an agreed Memorandum of Understanding was made in January 2020 prior to the NICE appraisal commencing and before the final scope for this appraisal was developed.

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.	.	.	[INSERT / DELETE ROWS AS REQUIRED]
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Deadline for comments **5:00pm on 10 March 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response	ERG response
Key issue 1: Inclusion of ezetimibe as part of standard care rather than as active comparator	**YES**	**1. Clinical feedback on the use of ezetimibe in clinical practice in England** Novartis asked twelve primary care physicians, including General Practitioners (GPs) with an extended role in cardiology, about the use of ezetimibe in clinical practice in England. All agreed that ezetimibe is not used extensively in clinical practice. The key reasons were perceived weak evidence of effectiveness, patient resistance, and a perception of ezetimibe as a secondary care option (appropriate for patients who are intolerant to statins, with familial hypercholesterolaemia [FH] or with more challenging low-	1) The ERG appreciates the company comments regarding the suggested low uptake of ezetimibe. However, the response is not necessarily of relevance when considering ezetimibe as a comparator to inclisiran. The drug is available on the market and can appear in the same place as ezetimibe; i.e., as a second line treatment for those in who LDL-C levels are not managed following maximally tolerated statin use, or as a first line treatment in those who cannot tolerate statins. The survey results presented by the company indicate that

		density lipoprotein cholesterol [LDL-C] management). Additional factors were a lack of incentives for LDL-C optimisation and a perceived gap between primary and secondary care. All experts (except one) reported very low ezetimibe prescribing (no more than 5% of patients receiving lipid lowering therapies), as evidenced by the patient share data discussed in part 2 below. One GP indicated more widespread use of ezetimibe but acknowledged that this is not the case nationally. Based on the feedback received, we believe our definition of standard of care as maximally tolerated statins with or without ezetimibe reflects real-world established NHS practice in England. Most GPs did not expect the use of ezetimibe to increase significantly. Key reasons were the lack of confidence in its efficacy and limited resources to	the primary care physicians (n=12) have a mixed interpretation of guidance for the use of ezetimibe. The ERG were unable to ascertain the representativeness of this sample of primary care physicians from the population in the NHS, or their conflicts of interest status. The perception of ezetimibe as an option only for secondary care further limits the rationale put forward by the company - that ezetimibe can be considered as part of SoC. Particularly as the company intend inclisiran to be positioned within the primary care segment of the treatment pathway. Patient resistance and limited resources to manage lipid optimisation in primary care are factors likely to affect all lipid lowering therapy options.

		manage lipid optimisation in primary care. The consensus of the primary care physicians, including a GP who is an advisor for NICE cardiology guidelines, was that ezetimibe is not a mandatory treatment step in the treatment pathway following inadequate response to maximally tolerated statins and prior to PCSK9 inhibitors. A more detailed summary of the primary care physicians' feedback is provided in Appendix 1.	Where patients are reluctant to try new treatments beyond their statin therapy, it could be argued that the prospect of an unknown injectable may possibly generate more resistance than the addition of an oral tablet to their daily regime. Similarly, with limited resources available, primary care providers need to maximise outcomes for patients by offering only the most cost-effective treatment options. 2) The ERG notes the patient share data presented by the company. However, the ERG consider that the suggested low uptake may also be linked to the prior costs surrounding ezetimibe (e.g., availability of generics, as described by the company). The cost of this drug has recently reduced due to

		2. Additional patient share data for ezetimibe and branded Ezetrol The patient share for ezetimibe (generics) and Ezetrol (brand) combined has accounted for less than 3% of the dyslipidaemia market in England since 2015 (approx. 223,000-247,000 patient equivalents) [1]. Subnational data for England in 2020 indicates some variability in the usage of ezetimibe and Ezetrol across England, ranging from 0.5% up to a maximum of 4.9% patient share for both agents combined. In England in 2020, 50% of bricks (small geographical areas) reported a patient share between 2% and 3% for ezetimibe and Ezetrol combined; only 7% of bricks had a patient share of ≥4%	expiry of the patent. This new lower cost has increased the cost-effectiveness of ezetimibe compared to SoC and may lead to increased uptake. Efficacy results from the company NMA show a [redacted] reduction in percentage LDL-C with ezetimibe at a treatment cost per patient of [redacted] per year. Given the limited uptake of ezetimibe proposed by the company, it is inconsistent to account for ezetimibe as a SoC for every patient. The ERG acknowledges that the uptake for ezetimibe is currently small. However, this suggested low uptake is in the context of widespread undertreatment of hypercholesterolaemia and dyslipidaemia throughout the UK. As highlighted by the company in Appendix 1 (primary care physicians' feedback), there are numerous barriers in the

		for ezetimibe and Ezetrol combined [2]. Ezetimbe was launched in 2003, received a NICE recommendation in 2008 and a revision in 2016 and continues to be used in only a small minority of patients. Despite generic versions of ezetimibe being available since 2018, its usage has not dramatically increased in England. Year-on-year growth for ezetimibe generics and Ezetrol combined was 4.7% in 2019 and 2.7% in 2020. This is roughly in line with the growth seen across the entire dyslipidaemia market in 2019 and 2020 (~4% and ~2%, respectively) [1]. At this point in time, there are no foreseeable market events that would suggest this is likely to change. This is in stark contrast to when Zocor and Lipitor went generic in 2003 and 2012 respectively; the use of generics to Zocor (simvastatin) and Lipitor	optimisation of lipid levels across the population and varied interpretation of guidance for use of ezetimibe among primary care practitioners. The ERG suggests that increased uptake of statins on patent-expiry, may largely be attributable to published NICE guidance CG181. This guidance specifies the use of atorvastatin for primary and secondary prevention of CVD and emphasises prescription of a high intensity statins at low acquisition cost on initiation of treatment. CG181 was published in 2014, replacing and updating guidance TA94 (2006). Additional patient groups and increased dosage recommendations were also included which are likely to have increased statin uptake from that point and be

		(atorvastatin) far exceeded the historic use of the respective branded products [3]. Furthermore, even rosuvastatin, which is a less frequently used statin in England, has witnessed 8-13% year-on-year growth following entry of generic versions of the molecule [1]. **3. Latest NICE guidelines** Current NICE guideline CG181 includes ezetimibe as an option that can be considered but does	reflected in the evidence highlighted by the company. 3) The ERG agrees with company response 3. This point demonstrates why ezetimibe cannot be considered as a step in the pathway prior to inclisiran and, therefore, should be considered as a comparator. 4) The ERG agrees with the companies' statement of findings that "statins represent the mainstay of

		not present it as a distinct step in the treatment pathway [4]. **4. Cost-effectiveness estimates including ezetimibe as an active comparator**	SoC". Whilst the proportion prescribed ezetimibe in addition may be small, it remains a treatment option at this stage. Therefore, inhabiting the same position in the treatment pathway as intended with inclisiran. The ERG maintains that ezetimibe is an active comparator and the relevant ICERs for decision-making are those which do not absorb its cost, and notably its efficacy, within SoC. When ezetimibe is treated as an active comparator the resulting ICERs presented for inclisiran + SoC more than [redacted] for both ASCVD and PPER populations: ASCVD results from company PSA [redacted] PPER results from company PSA [redacted]

		Novartis is committed to bringing inclisiran to the market at a price that offers exceptional value versus the real-world standard of care (SoC). As confirmed by clinical experts, statins represent the mainstay SoC with a very small proportion of patients additionally receiving ezetimibe. We therefore continue to consider that our base case analysis, in which SoC is defined as maximally tolerated statins with or without ezetimibe, is the most appropriate for decision-making. However, in response to the ERG request to consider ezetimibe as an active comparator, we have provided scenario analyses in Appendix 2. These represent cost-effectiveness results that are relevant to the small proportion of patients who are receiving statins and ezetimibe in clinical practice. [redacted]	[redacted] The increase in ICER is mainly due to the efficacy of ezetimibe demonstrated through a smaller difference in QALYs produced by inclisiran, when compared to ezetimibe + SoC rather than SoC alone. ASCVD QALY difference between inclisiran + SoC and: [redacted] (ezetimibe + SoC) [redacted] (SoC) PPER QALY difference between inclisiran + SoC and: [redacted] (ezetimibe + SoC) [redacted] (SoC)

		[redacted] Please note the proportion of ezetimibe usage within SoC in the cost-effectiveness model is informed by the ORION trials (c. 50-56%, 10% and 6-8% in ORION-9, -10 and -11, respectively [5-7]). This represents a conservative approach to the definition of SoC as ezetimibe usage in the trials was higher than current usage in UK clinical practice. **Conclusion** The guide to the methods of technology appraisal states that the Committee will normally be guided by established practice in the NHS when identifying the most appropriate comparator(s) [8]. Current NICE guideline CG181 demonstrates that ezetimibe is not an additional step in the treatment pathway [4]. Given the feedback from primary care physicians and the patient share data presented above,	The results presented by the company (based on efficacy values obtained in the company NMA, upon which they rely for this submission) demonstrate that ezetimibe is a cost-effective option for treating hypercholesterolaemia in these populations, when compared to SoC, at this point in the treatment pathway. The ERG have considered the results of the scenario analyses provided by the company in Appendix 2. The ERG has replicated the deterministic results presented for all scenario analyses based on the 2 main populations as well as results for the subgroup populations (ASCVD and PPER statin intolerant and ASCVD high risk LDL-C level >4.0mmol/L).

		there is no reason to believe that ezetimibe usage will increase in the future. Considering the very low and somewhat variable current use of ezetimibe and that, based on the clinical feedback received, ezetimibe is likely to continue being used only for a very small minority of patients in the future, we believe our definition of SoC as maximally tolerated statins with or without ezetimibe reflects established clinical practice in the real-world. It is therefore the most suitable basis for decision-making on the cost-effectiveness of inclisiran.	The ERG is cautious surrounding the true validity of results obtained due to technical errors within the model (discussed in Appendix 5). Whilst results appear sensible, given the sensitivity of the model to baseline characteristics, the ERG are not confident in the exact figures presented. The ERG were able to run PSAs for ASCVD and PPER populations and are satisfied the results presented by the company are representative of probabilistic ICER ranges. The ERG is concerned that ICERs for the ASCVD and PPER populations with serum [redacted] are obtained using mean LDL-C levels of [redacted] and [redacted] mmol/L, respectively. NICE recommendations for use of alirocumab and evolocumab are defined by levels of severity in the ASCVD

			population: high risk ≥4.0 mmol/L and very high risk CVD serum LDL-C ≥3.5. Therefore, the mean LDL-C level of [redacted] used for the whole ASCVD population is already extremely close to the severity reference threshold for use of PCSK9 inhibitors and may significantly overestimate the cost-effectiveness of inclisiran in the ASCVD population with mean serum LDL-Cs between [redacted] mmol/L. The ERG considers results of subgroup analyses further in Appendix 5 with reference to baseline characteristics of the modelled subgroups highlighted. The ERG undertook scenario analyses for additional subgroups ASCVD serum LDL-C ≥1.8, ≥2.2, ≥3.0 and ≥3.5mmol/L to determine the effect of varying baseline mean LDL-C levels on the ICER. Results

are presented below in table 1 with full details reported in Appendix 5, table 1.

Table 1. ICER results for ASCVD subgroups by severity (serum LDL-C mmol/L)

ASCVD subgroup minimum LDL-C	ASCVD subgroup mean LDL-C	ICER inclisi SoC v ezetir SoC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The ERG believes the mean LDL-C of ASCVD patients with LDL-C [redacted] and [redacted] mmol/L from the ORION-10 & -11 trials is closer to the 3.07mmol/L mean found in [redacted] mmol/L subgroup. This suggests an ICER nearer

			[redacted] is more representative in this population. Confirmation from the company is also sought to establish baseline characteristics of the very high risk CVD serum LDL-C ≥3.5mmol/L cohort modelled. At the NICE submission Advisory Board Meeting, July 2020, the board were clear in their directions with consensus from both clinical and health economics perspectives that NICE guidelines treat ezetimibe as an active comparator. The ERG note that NICE appraisals for alirocumab (TA393), evolocumab (TA394) and bempedoic acid (GID-TA10534), all of which are listed as comparators in the inclisirsan final scope, treat ezetimibe as an active comparator. The company submission relies heavily on the TA393 submission to justify their approach to

			modelling. However, the ERG highlights the omission of ezetimibe as an active comparator, which marks a notable departure from TA393. As the current NICE guideline CG181 does not stipulate ezetimibe as an additional step in the treatment pathway, the ERG affirm its position as an active comparator to inclisiran. Usage levels of ezetimibe are not grounds to preclude it as an active comparator. Primary care physicians responses to the company's survey indicated zero percent of patients seen received PCSK9 inhibitors (Appendix 1). Similarly, the bempedoic acid appraisal committee the patient and clinical expert noted that uptake of alirocumab and evolocumab in clinical practice is between 65% and 72% lower than expected.(ERG 1) The ERG note the company did not exclude PCSK9 inhibitors from their evaluation.

			Respondents to the company survey (Appendix 1) suggested that projects currently in development which aim to improve cardiovascular disease prevention and push primary prevention more and the new NICE Rapid Uptake Product (RUP) guidance for lipid management are likely to increase the use of statins over the next 3 years.(ERG2) The ERG note that ezetimibe is explicitly identified, along with high intensity statins and PCSK9 inhibitors, as medicines along the evidence-based pathway that RUP initiatives aim to maximise use of in order to improve lipid profiles of the population.(ERG3) The ERG considers these are mechanisms by which uptake of ezetimibe may be increased over future years.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG response
Additional issue 1: Generalisability of the results from the ORION-10 and ORION-11 studies	Page 12	**NO**	Patient characteristics in the ORION trials are broadly comparable with patient characteristics in the CPRD study using the ARUM database (as presented in the submission), which contains records on approximately 13 million currently registered patients (23% of the total English population) (Table 1 and Table 2). There are some discrepancies (e.g. the proportion of diabetic patients), but the forest plots presented in the submission and the ORION trial publications demonstrate the **constant effectiveness of inclisiran** across subgroups, which provides reassurance regarding the generalisability of the ORION trials to the UK population.	The ERG disagrees with the company's assertion that patients from the ORION trials are broadly comparable with patient characteristics in the CPRD study. Comparing tables 1 and 2 and using the "PPER and serum LDL-C ≥2.6 mmol/L" population as an example, females comprised 54% of the population in the ORION trials versus 33% in the CPRD study; also, the proportion of patients with diabetes was 66% (ORION trials) vs 15% (CPRD study). However, the ERG agrees that the forest plots show that the effectiveness of inclisiran does not vary across subgroups. The ERG agrees with the comment from Amgen that "Results from ORION-10 (and also ORION-11) cannot be considered

Table 1: Patient characteristics in the ORION trials

Population		Age	% female	% diabetes	LDL-C (mmol/L)
Secondary prevention	ASCVD and serum LDL-C ≥2.6 mmol/L†	64.75	34%	38%	3.47
Primary prevention	PPER and serum LDL-C ≥2.6 mmol/L‡	62.28	54%	66%	4.02
	HeFH without ASCVD and serum LDL-C ≥2.6 mmol/L¶	52.36	58%	7%	4.09

†Source: patients with ASCVD in ORION-10 and -11; ‡Source: patients with PPER in ORION-11; ¶Source: patients in ORION-9.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease;.LDL-C, low-density lipoprotein cholesterol; PPER, primary prevention with elevated risk.

generalisable to patients with a recent atherosclerotic cardiovascular disease (ASCVD) event, since the studies excluded patients with a major cardiovascular (CV) event within 3 months prior to randomisation. Given these patients are at an increased risk of subsequent ASCVD (see Additional Issue 4), they require therapies providing rapid low density lipoprotein-cholesterol (LDL-C) lowering. Including these patients in the ASCVD base case when estimating risks from the Clinical Practice Research Datalink (CPRD) may overestimate the efficacy of inclisiran."

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<td>Table 2: Patient characteristics in the CPRD study
<table>
<tr><th colspan="2">Population</th><th>Age</th><th>% female</th><th>% diabetes</th><th>LDL-C</th></tr>
<tr><td>Secondary prevention</td><td>ASCVD and serum LDL-C ≥2.6 mmol/L</td><td>68.77</td><td>45%</td><td>16%</td><td>3.47</td></tr>
<tr><td rowspan="2">Primary prevention</td><td>PPER and serum LDL-C ≥2.6 mmol/L</td><td>65.73</td><td>33%</td><td>15%</td><td>3.63</td></tr>
<tr><td>HeFH without ASCVD and serum LDL-C ≥2.6 mmol/L</td><td>52.62</td><td>64%</td><td>2%</td><td>4.75</td></tr>
</table>
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CPRD, Clinical Practice Research Datalink; LDL-C, low-density lipoprotein cholesterol; PPER, primary prevention with elevated risk.</td>
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<td>Additional issue 2: lack of genetic testing results in some</td>
<td>Page 21</td>
<td>NO</td>
<td>We fully agree that there is an issue with the lack of genetic testing in clinical practice. Our understanding, as confirmed by clinical experts, is that patients are often coded as having FH by GPs when FH is suspected;</td>
<td>The ERG and company seem to be in agreement with regards to additional issue 2. The ERG points out this could lead to both overestimating the number of cases and also missing some asymptomatic cases who do</td>
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FH cases being missed			however, this is often never confirmed as genetic testing is not required. Therefore, the population of patients with FH in the CPRD study is likely an overestimate. Additionally, there is no distinction in the CPRD database between homozygous and heterozygous FH (HeFH). This leads to heterogeneity within the cohort labelled as FH in the CPRD study and hence uncertainty in their CV event rates. Additionally, patients with FH would also be classified into the other two population groups (i.e. primary prevention with elevated risk (PPER) or ASCVD). Our submission explains that the groups are not mutually exclusive; patients with FH would fall into the PPER or ASCVD category based on whether they have experienced a cardiovascular (CV) event.	not quite meet the existing criteria. The ERG has no issues with what the company has done with regards to this point.
Additional issue 3: lack of a scenario analysis using event rates from Beliard, 2018 because of technical errors in the	Page 135	**YES**	The requested scenario analysis for the HeFH secondary prevention population is presented below. Beliard 2018 reports the rate of recurrent CV events in patients with secondary prevention HeFH as 9 per 100 patient years [9]. Of 511 observed events there were 36 myocardial infarctions, 31 unstable angina, 76 peripheral arterial disease, 8 CV deaths and 30 strokes,	The ERG supports the figures extracted by the company from the Beliard 2018 study to inform baseline CV event rates and is satisfied with the results obtained in the scenario analysis provided. The ICER of [redacted] per QALY for inclisiran is marginally [redacted] that the [redacted]. The ERG considers both ICER

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<td>company's economic model</td>
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<td>with the rest being revascularisations. Table 3 presents the resulting annual event probabilities used in the model.

Table 3: Annual event probabilities calculated using Beliard 2018
<table>
<tr><th>MI</th><th>UA</th><th>Stroke</th><th>Revascularisation</th><th>CV death</th></tr>
<tr><td>0.00632</td><td>0.005445</td><td>0.00527</td><td>0.056465</td><td>0.001408</td></tr>
</table>
Abbreviations: CV, cardiovascular; MI, myocardial infarction; UA, unstable angina.

The mean age of patients in the study was 60. No baseline LDL-C is reported, however, a mean LDL-C of 144 mg/dL is reported as the mean final value at last clinic visit; this was used to inform the model.

Results using Beliard 2018 to inform baseline CV event rates in the HeFH secondary prevention population are presented in Table 4.
[redacted]

Ezetimibe was not included in this analysis as it was not possible to include ezetimibe in the NMA for HeFH, due to an absence of data on ezetimibe's efficacy in this population (Company submission Appendix D).</td>
<td>values presented are more plausible than the [redacted] result obtained using the CPRD analysis event probabilities. However, the ERG suggest that Beliard 2018 results are more representative due to the study's larger sample size, methodology and considerably more recent publication date.

The ERG understands that ezetimibe was not included in this analysis due to an absence of data on ezetimibe's efficacy in this population which could be used to inform the company's NMA.

The ERG reiterates from our statement above (4); for the ASCVD and PPER populations, the inclusion of ezetimibe as an active comparator has the effect of approximately [redacted] the ICER for inclisiran compared to when ezetimibe is included as part of SoC. Whilst we acknowledge that the same effect cannot be assumed in this population, it is indicative that if ezetimibe were to be included, we would likely anticipate [redacted] in the ICER.</td>
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<td>Table 4: Cost-effectiveness results in secondary prevention HeFH using Beliard 2018 event rates
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<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incr. costs (£)</th><th>Incr. LYG</th><th>Incr. QALYs</th><th>ICER versus baseline (£/QALY)</th><th>ICER incr. (£/QALY)</th></tr>
<tr><td>SoC</td><td>  </td><td>  </td><td>  </td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Inclisiran + SoC</td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
<tr><td>Alirocumab + SoC</td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
<tr><td>Evolocumab + SoC</td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td><td>  </td></tr>
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Abbreviations: HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SoC, standard of care.</td>
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<tr>
<td>Additional issue 4: The</td>
<td>Page 107</td>
<td>YES</td>
<td>See Appendix 3</td>
<td>As described in Table 15 of the ERG report, the inconsistency in definitions and poor reporting coupled with small number of</td>
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impact of differences in CV risk and severity of patients within each population strata of interest (i.e., HeFH and ASCVD) on the relative effects observed for efficacy outcomes focused on changes in LDL-C, HDL-C, and discontinuations				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. (Most studies in the NMA included either participants with history of CV (ASCVD) event, those with risk equivalent (ASCVD-RE or PPER), or both groups. However, studies used inconsistent definitions and criteria for categorizing CV risk which may have led to some variability in the distribution of CV risk across the trials in NMA.) In their submission the company assume 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. However, the ERG wishes to reiterate that the limitation in evidence complicates any type of comparison for CV risk. In an attempt to explore the impact of differences in CV risk and severity of patients within each population strata of interest the

				company present a [redacted] (Appendix 3 [4]). Based on Appendix 3 Table 2, the ERG agrees that baseline LDL-C (as a proxy for cardiovascular risk) [redacted] the percentage change in the level of LDL-C level after 24 weeks following administration of inclisiran versus other treatments. The results presented are [redacted] with the base case results (see Table 2, Appendix 3).
Additional issue 5. Request for SUCRA plots and treatment ranking	Page 109	**YES**	See Appendix 3	The ERG would like to thank the company for Appendix 3 (5). The SUCRAs and treatment ranking (%) have been assessed and are considered to be appropriate. As suggest by the company the [redacted]
Additional Issue 6:	Page 16	**YES**	See Appendix 3	The ERG have examined Appendix 3 (6, NMA scenarios wherein ORION-10 and

Request for NMA scenarios wherein ORION-10 and ORION-11 were not pooled (i.e. separate analyses were conducted based on each inclisiran trial)				ORION-11 were not pooled) and note the following; When excluding ORION-10, all the estimates are [redacted] towards inclisiran. However, there is [redacted]. This does [redacted] the probability that inclisiran is [redacted] compared to the active treatments, but there was [redacted] When excluding ORION-11, all of the estimates are now [redacted] towards inclisiran, but with [redacted]. Alirocumab is now [redacted] compared to inclisiran. There is [redacted] compared to inclisiran. This has [redacted] across all of the treatments. In summary, the ERG is in alignment with the company statement that [redacted]. The ERG note that excluding one trial makes the results more favourable, excluding the other trial makes the results less favourable.

				However, there were [redacted]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Not applicable – the estimates are unchanged.

References

1. *Patient equivalent numbers derived from IQVIA C10 data cube, Hospital Retail Combined Trawling Data, Yearly Unit Sales.* 2020.
2. *Patient shares derived from IQVIA C10 data cube, HPA Sub National Data, Monthly Unit Sales.* 2019-2020.
3. Chapman, S.R., R.W. Fitzpatrick, and M.I. Aladul, *Has cost inhibited the uptake of more potent statins in England?* Pharmacoepidemiology and Drug Safety, 2017. **26**(8): p. 984-991.
4. National Institute for Health and Care Excellence, *CG181: Cardiovascular disease: risk assessment and reduction, including lipid modification. Available at: https://www.nice.org.uk/guidance/cg181 (last accessed 9th April 2020).* 2016.
5. Data on file [INC-DOF-007], *ORION-10 Clinical Study Report.*
6. Data on file [INC-DOF-008], *ORION-11 Clinical Study Report.*
7. Data on file [INC-DOF-006], *ORION-9 Clinical Study Report.*
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ERG3. https://www.england.nhs.uk/aac/what-we-do/what-innovations-do-we-support/rapid-uptake-products/

ERG TE: Appendix 5

The company provided results for the whole ASCVD population defined as those with ASCVD serum LDL-C ≥2.6mmol/L and scenario analyses for subgroups of this population with high risk serum LDL-C >4.0mmol/L and very high risk CVD serum LDL-C ≥3.5mmol/L. These subgroups are aligned with NICE recommendations for the use of PCSK9 inhibitors in TA393 and TA394.

The ERG were able to replicate results for the LDL-C ≥2.6mmol/L and high risk LDL-C >4.0mmol/L populations in the updated model provided. A different set of events risks for the very high risk CVD serum LDL-C ≥3.5mmol/L were taken from CPRD data but not transposed to risks for baseline characteristics from ORION trial data. The ERG are seeking to confirm with the company the baseline characteristics used to produce the ICER results provided, as they have not yet been validated within the model.

The ERG undertook additional subgroup analyses based on a range of severity levels of serum LDL-C to assess the impact of changes in baseline mean LDL-C levels on the ICER for inclisiran + SoC vs ezetimibe + SoC. Results are presented in Table 1.

Table 1. Baseline demographics and cost-effectiveness estimates for ASCVD population subgroups defined by severity (serum LDL-C mmol/L)

Sub-group	ERG scenario analyses for additional subgroups and validation of company subgroup analysis						Company scenario analysis
	ASCVD serum LDL-C ≥1.8mmol/L	ASCVD serum LDL-C ≥2.2mmol/L	ASCVD serum LDL-C ≥2.6mmol/L	ASCVD serum LDL-C >3.0mmol/L	ASCVD serum LDL-C >3.5mmol/L	ASCVD high risk serum LDL-C >4.0mmol/L	*Very high risk CVD serum LDL-C ≥3.5mmol/L
Baseline characteristics	ORION-10 & -11	ORION-10 & -11	ORION-10 & -11	ORION-10 & -11	ORION-10 & -11	ORION-10 & -11	CPRD analysis
Mean age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% diabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean LDL-C (on maximally tolerated statins)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ezetimibe + SoC vs Inclisiran + SoC							
Incremental Costs vs baseline (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs vs baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).

Mean baseline LDL-C levels for ASCVD subpopulations defined by minimum severity of LDL-C levels are substantially higher than minimum values for the subgroup, with an average difference of 0.9mmol/L. As mean LDL-C levels increase, ICER values decrease thereby increasing the cost-effectiveness of inclisiran + SoC vs ezetimibe + SoC.

Deterministic ICER results for the ASCVD serum LDL-C ≥2.6mmol/L are based on a mean LDL-C level of [redacted] and produce an ICER of [redacted]. However, preliminary analysis of patient level data from ORION-10 and -11 clinical trials by the ERG indicates that the mean LDL-C level for the ASCVD population with LDL-C [redacted] is [redacted] (See Table 2). The ERG seek to confirm these preliminary results, but initial findings suggest the ICER value for the ASCVD population not defined as high risk by NICE (i.e. LDL-C [redacted]) is likely to lie nearer to the value obtained for the ≥2.2mmol/L subgroup (see Table 1) at approximately [redacted] per QALY.

Table 2. Preliminary analysis of ASCVD patient characteristics from ORION 10 & -11 with baseline serum LDL-C [redacted]

ASCVD patients ORION-10 & -11 with baseline serum [redacted]					[redacted]
Mean age			Mean LDL-C		
[redacted]			[redacted]		
Female			Diabetes		
[redacted]			[redacted]		

Preliminary analysis of ORION trial data for the PPER population (termed ASCVD-RE within the trial literature) was also conducted by the ERG. The mean LDL-C for the PPER population serum [redacted] is [redacted]. However, when restricted to the subgroup population with baseline serum [redacted], mean LDL-C is substantially lower at [redacted] (See Table 3).

Table 3. Preliminary analysis of PPER patient characteristics from ORION -11 with baseline serum [redacted]

PPER patients ORION-11 with baseline serum LDL-C [redacted]					[redacted]
Mean age			Mean LDL-C		
[redacted]			[redacted]		
Female			Diabetes		
[redacted]			[redacted]		

Statin Intolerant Populations

The ERG compared the results for ASCVD and PPER whole population with those of their statin intolerant subgroups from, examining the baseline demographics from the relevant ORION trials (see Table 4).

Statin intolerant patients in ASCVD and PPER populations had higher baseline LDL-C than their overall ASCVD and PPER populations (4.17mmol/L vs 3.45mmol/L and 5.19 mmol/L vs 4.05 mmol/L, respectively). In validating company results the ERG noted this was mis-stated

as 5.00 mmol/L vs 4.02 mmol/L for the PPER population in company Appendix 2, but all other results were correct).

The higher baseline LDL-C levels in statin intolerant populations drives a reduction in ICER values for these subgroups relative to the overall population.

For ASCVD statin intolerant patients the ICER for inclisiran + SoC vs ezetimibe + SoC is cost effective at a WTP threshold of £20,000/QALY at [redacted]. However, for PPER statin intolerant patients the ICER is just above this WTP threshold at [redacted].

Table 4. Baseline demographics and cost-effectiveness estimates for ASCVD and PPER populations compared with their statin intolerant subgroups

Sub-group	ASCVD population Whole population (Statins & no statins)	ASCVD population Statin intolerant (no statins)	PPER population Whole population (Statins & no statins)	PPER population Statin intolerant (no statins)
Baseline characteristics	ORION-10 & -11	ORION-10 & -11	ORION-11	ORION-11
No. of patients	[redacted]	[redacted]	[redacted]	[redacted]
Mean age	[redacted]	[redacted]	[redacted]	[redacted]
% female	[redacted]	[redacted]	[redacted]	[redacted]
% diabetes	[redacted]	[redacted]	[redacted]	[redacted]
Mean LDL-C (on maximally tolerated statins)	[redacted]	[redacted]	[redacted]	[redacted]
Ezetimibe + SoC vs Inclisiran + SoC				
Incremental Costs vs baseline (£)	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs vs baseline	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	[redacted]	[redacted]	[redacted]	[redacted]

Technical errors identified in company model ID1647 Inclisiran Novartis TE responses CEM v4.7 11032021KM [ACIC]

The ERG are cautious surrounding the true validity of results obtained. Whilst results appear sensible, given the sensitivity of the model to baseline characteristics, the ERG are not confident in the exact figures presented due to technical anomalies identified within the model:

- Alterations to “PLD” sheet to specify correct cohort for scenario analysis feeds through to “key results” sheet initially for demographic baseline data except minimum LDL-C in mg/dL but reverts back to ASCVD-RE demographic baseline when ASCVD results are calculated leaving it unclear as to which figures are used.
- Some cells displayed negative values in the engine worksheets.

- Cells C12-14 “sensitivity analysis” sheet do not update from “individual population data” results sheet cells I16-18, respectively.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

Company evidence addendum

- The committee has focused on the incremental analysis versus ezetimibe and consider there may be too much uncertainty at the previously proposed price of [redacted] per patient per maintenance year, to recommend Inclisiran for the full ASCVD cohort with >2.6 mmol/L.

- Despite Novartis disagreement with ezetimibe as the most relevant comparator, in the spirit of collaboration that will be needed to realise the collective ambitions for Inclisiran, we will offer a final reduced price of [redacted] per patient per maintenance year to address committee's concerns.

- As can be seen in Table 1 below, this price revision leads to cost-effectiveness results in the fully incremental analyses versus ezetimibe that are within standard ranges, and exceptional value in the pairwise analyses which consider inclisiran as add-on therapy to real-world current standard care (maximally tolerated statins + up to 10% ezetimibe).

Table 1: ASCVD population ICER table illustrating the impact of the revised offer on the cost-effectiveness results

		Commercial agreement price ([redacted])	**Revised price ([redacted])**
Pairwise comparison vs current NHS real-world practice (maximally tolerated statins + up to 10% ezetimibe)	Whole ASCVD population > 2.6	[redacted]	[redacted]
	High risk patients ineligible for PCSK9s (>2.6, <4.0)	[redacted]	[redacted]
	Very high risk patients ineligible for PCSK9s (>2.6, <3.5)	[redacted]	[redacted]
Fully incremental analysis vs ezetimibe	Whole ASCVD population > 2.6	[redacted]	[redacted]
	High risk patients ineligible for PCSK9s (>2.6, <4.0)	[redacted]	[redacted]
	Very high risk patients ineligible for PCSK9s (>2.6, <3.5)	[redacted]	[redacted]