Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Contents:

The following documents are made available to stakeholders:

Attendees can find the **scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Ultragenyx

2. **Company summary of information for patients (SIP)** from Ultragenyx

3. **Clarification questions and company responses:**
   a. Main response
   b. Appendix to question A16

4. **Patient group, professional group and NHS organisation submissions** from:
   a. HEART UK – patient perspectives
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5. **External Assessment Report** prepared by BMJ-TAG

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Post-technical engagement documents

7. **Technical engagement response from company:**
   a. Main response
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8. **Technical engagement responses and statements from experts:**
   a. Jaimini Cegla, Consultant in Metabolic Medicine – clinical expert, nominated by HEART UK
   b. Karen Hasid, HEART UK Ambassador – patient expert, nominated by HEART UK

9. **Technical engagement responses from stakeholders:**
   a. British Cardiovascular Society – endorsed by Royal College of Physicians

10. **External Assessment Report critique of company response to technical engagement** prepared by BMJ-TAG

11. **External Assessment Group addendum – deterministic and probabilistic ICERs**

12. **Clinical expert responses to query on treatment pathway** from NICE technical team:
    a. Jaimini Cegla
    b. Handrean Soran
        i. Main response
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Single technology appraisal

Evinacumab for the treatment of homozygous familial hypercholesterolaemia ID 2704

Document B

Company evidence submission

May 2023

File name	Version	Author	Description	Contains confidential information	Date
ID2704_evinacumab company evidence submission_Document B_26052023_redacted	1.0	Ultragenyx	Document B final submitted version for B1, B2 and B3	Yes (fully redacted)	26/05/2023

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Abbreviations

AE	Adverse event
ANGPTL3	Angiopoietin-like protein 3
Apo	Apolipoprotein [type]
BMI	Body mass index
CEM	Cost-effectiveness model
CHD	Coronary heart disease
CI	Confidence interval
CTT	Cholesterol Treatment Trialists'
CV	Cardiovascular
CVD	Cardiovascular disease
CSR	Clinical study report
DBTP	Double-blind treatment period
EAS	European Atherosclerosis Society
FDA	Food and Drug Administration
EMA	European Medicines Agency
FH	Familial hypercholesterolaemia
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HoFH	Homozygous familial hypercholesterolemia
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
KM	Kaplan-Meier
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LDRAP1	Low-density lipoprotein receptor adaptor protein 1
LPL	Lipoprotein lipase
LLT	Lipid lowering therapy
LOF	Loss of function
LOCF	Last observation carried forward
LS	Least squares
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MR	Magnetic resonance

MTP	Microsomal triglyceride transfer protein
NAb	Neutralising antibody
NICE	National Institute for Health and Care Excellence
OLTP	Open label treatment period
OWSA	One-way sensitivity analysis
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
PLD	Patient level data
QALY	Quality-adjusted life year
QoL	Quality of life
SA	Stable angina
SAE	Serious adverse event
SF-36	Short Form 36
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TIA	Transient ischaemic attack
TC	Total cholesterol
TG	Triglycerides
UA	Unstable angina
VEGF	Vascular endothelial growth factor
VLD-C	Very low-density lipoprotein cholesterol

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

B.1.1 Decision problem

The objective of this submission is to appraise the clinical and cost-effectiveness of evinacumab, covering its full marketing authorisation, as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolaemia (HoFH) (1). Evinacumab is licensed for this purpose in the United Kingdom, with marketing authorisation issued in August 2022.

Further details of the decision problem are shown 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 homozygous familial hypercholesterolaemia aged 12 years and over	Unchanged	N/A
Intervention	Evinacumab as an adjunct to diet and other LDL-C lowering therapies	Unchanged	N/A
Comparator(s)	**For people aged 18-years and older:** Established clinical management without evinacumab (including but not limited to statins, diet and lifestyle changes, ezetimibe, lomitapide, evolocumab and LDL apheresis) **For people aged 12-17:** Established clinical management without evinacumab (including but not limited to statins, diet and lifestyle changes, ezetimibe, evolocumab and LDL apheresis)	**For people aged 18-years and older:** Lomitapide **For people aged 12-17:** No comparator is considered	The company believes the current comparator does not accurately describe the decision problem, as it implies that evinacumab is intended for use as an addition to lomitapide, whereas in fact evinacumab is primarily intended to *replace the use of lomitapide*. **For people aged 18 years and older**, lomitapide is currently positioned as a third-line treatment by 2014 EAS consensus guidelines (after statins, ezetimibe, PCSK9 inhibitors where indicated, LDL apheresis where indicated) (2). The NHS England commissioning policy document places lomitapide in the same position of the pathway (3), with lomitapide recommended for use in this context. The most recent EAS consensus statement (published 2023) recommends lomitapide and/or evinacumab with or without LDL apheresis as third-line treatment (4) (This is discussed further in Section B.1.3.6 Patient management pathways). There are no robust data published on the combined use of lomitapide and evinacumab.

			Whilst there are no known negative drug-drug interactions associated with the concomitant use, both drugs having different mechanisms of action would likely have an additive effect (5). It is expected however that the combination of treatments would not be offered on the NHS as it would be prohibitively expensive. Lomitapide is also associated with numerous very common GI and common hepatic AEs and tolerability issues that are not reported for evinacumab Lomitapide is also associated with AEs and tolerability issues (6) that are not experienced with evinacumab (1). The company contends that evinacumab should therefore be a replacement for, rather than an addition to, lomitapide in adults for the reasons discussed in this submission document. **For people aged between 12 and 17 years**, evinacumab is indicated, in contrast to lomitapide which is not indicated in this population. However, there are only very limited comparative evidence for this group (2 subjects enrolled in the ELIPSE trial were in this age range), with most evidence being limited to single-armed data only. For this reason, the use of evinacumab in this age group will be considered in the clinical effectiveness element of the submission (where there is a significant unmet need in this population, see Section B.2.7.4 Use in adolescent patients), but will not be considered in the cost-effectiveness analysis.
Outcomes	The outcome measures to be considered include: • plasma lipid and lipoprotein levels, including LDL-C, non-	Unchanged	N/A

	HDL cholesterol, 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.		
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. 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.	The economic analysis is fully consistent with the NICE reference case	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered:	Only analysis on the clinical effectiveness (and safety) of evinacumab in these subgroups will be undertaken.	**People aged 12 to 17 years inclusive:** there are only very limited comparative evidence in this subgroup which is insufficient

	• People aged 12 to 17 years inclusive • Presence or level of risk of cardiovascular disease • Mutational status (e.g., LDLR status, compound heterozygotes, double heterozygotes)		to allow for robust cost effectiveness analysis. **Presence or level of risk of cardiovascular disease**: all patients with HoFH are considered to be at high risk of cardiovascular disease. Management is determined by target drug commencement and titration to achieve LDL-C levels (Section B.1.3.6 Patient management pathways), not overall assessment of cardiovascular risk. **Mutational status (e.g., LDLR status, compound heterozygotes, double heterozygotes)**: evinacumab is effective in all patients with HoFH, regardless of the underlying genetic mutation. This is also true for lomitapide. However, this is not true for all background treatments.
Special considerations including issues related to equity or equality	None listed in the final scope.	The use of evinacumab in people aged 12 to 17 years (inclusive) raises potential equity issues.	As noted, lomitapide, the only other effective pharmacological treatment available as third-line treatment, is not indicated in this age group. Thus, there is currently an unmet need in this age group that needs to be addressed. Age is a protected characteristic (7).

B.1.2 Description of the technology being evaluated

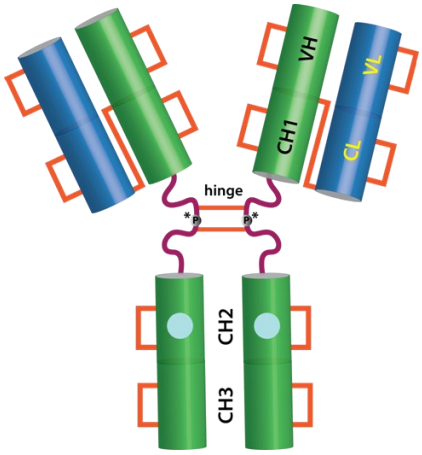
Summary

- Evinacumab is a novel, innovative, first-in-class drug indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolaemia (HoFH).
- It is a recombinant human monoclonal antibody which specifically binds to and inhibits angiopoietin-like protein 3 (ANGPTL3), a key regulatory protein involved in lipid metabolism in the liver. Inhibition of ANGLPTL3 reduces levels of circulatory LDL-C, TG, HDL-C, and other lipoproteins.
- Evinacumab reduces LDL-C independent of the presence of LDL receptors (LDLR). Its mechanism of action is independent of pathways targeted by other forms of lipid-lowering therapy (LLT), including statins and PCSK9 inhibitors. This means evinacumab has the potential to treat variants of HoFH that are not responsive to these treatments.
- Evinacumab is administered as an intravenous infusion over 60 minutes (15 mg/kg) once monthly (every 4 weeks). It is intended initially to be prescribed through specialised centres and administered in outpatient settings.

B.1.2.1 Mechanism of action

Evinacumab-dgnb (EVKEEZA®), herein referred to as evinacumab, is a fully humanised recombinant monoclonal antibody that has been developed as a targeted treatment for homozygous familial hypercholesterolaemia (HoFH). The molecular structure of the drug is presented in **Error! Reference source not found.**.

Figure 1. Molecular structure of evinacumab.



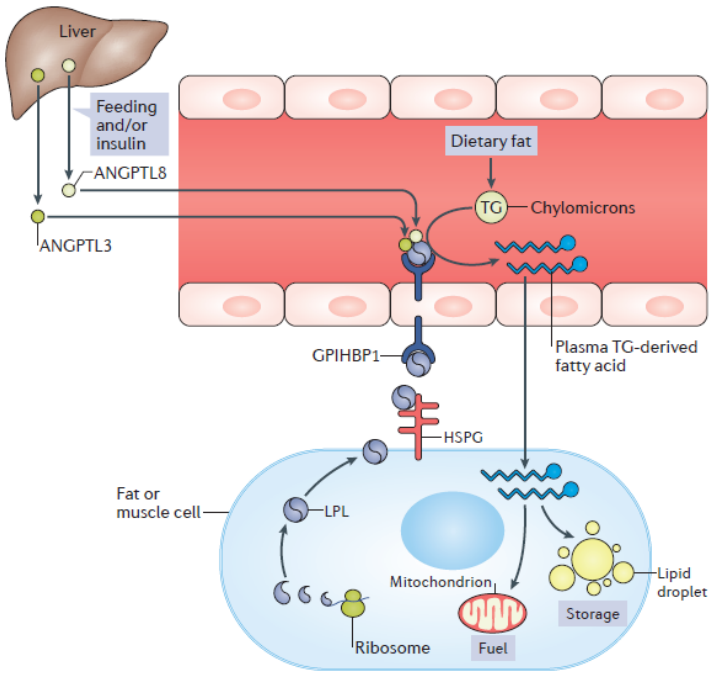
Legend: The figure above is a representation of the structure of evinacumab depicting the location of each of the intra-chain and inter-chain disulphide bonds (orange). Heavy (green) and light (blue) chains are connected by inter-chain disulphide bonds; heavy-chain dimerization is achieved through two heavy-chain intermolecular disulphide bonds located within the hinge region. The hinge region mutation (Ser234 to Pro234) is located between the two hinge region disulphide bonds and is annotated as P*. The Fc domain glycosylation site is also indicated (cyan) [6]. Original figure developed by Regeneron Pharmaceutical Inc. Permission has been sought.

Angiopoietin-like protein 3 (ANGPTL3), a member of the vascular endothelial growth factor (VEGF) family, is expressed primarily in the liver. It plays a prominent role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL) (8); two key enzymes that catalyse the partial hydrolysis of core triglycerides (TGs), very-low-density lipoprotein cholesterol (VLDL-C), chylomicrons, and high-density lipoprotein phospholipids, respectively (9). The functional effect of ANGPTL3, through inhibition of LPL and EL, counteracts this effect, increasing circulating lipid levels (10). An overview of the role of ANGPTL3 in respect to lipid metabolism is illustrated **Error! Reference source not found.**.

Evinacumab specifically binds to and inhibits ANGPTL3. This leads to reduction in LDL-C, HDL-C, and TGs, mirroring the lipid phenotype observed in humans with ANGPTL3 loss of function (LOF). Its use has been investigated for the treatment of HoFH, a rare genetic condition characterised by severely high levels of LDL-C (Section B.1.3.3 Disease progression and prognosis).

Evinacumab reduces LDL-C levels independently of low-density lipoprotein receptors (LDLRs) by promoting VLDL processing and clearance upstream of low-density lipoprotein (LDL) formation. Evinacumab blockade of ANGPTL3 lowers TG and HDL-C levels by rescuing LPL and EL activities, respectively (10). The mechanism of evinacumab in LDL-C reduction lowers the risk of an individual developing atherosclerosis and thus lowers the overall risk of cardiovascular disease (CVD) and associated mortality. Results from early studies showed that evinacumab has the potential to result in clinically significant LDL-C reductions in patients with HoFH (11, 12). A summary of the key characteristics of evinacumab are reported in Table 2.

Figure 2. Overview of the role of ANGPTL3 in plasma TG metabolism.



Legend: Dietary fat is transported through the blood as part of chylomicrons. The TGs in the chylomicrons are hydrolysed by LPL. LPL is produced by muscle cells and fat cells and is attached to the cell surface via heparan sulphate proteoglycans. The protein GPIHBP1 transports LPL from the cell surface to the capillary endothelium. ANGPTL3 is produced in the liver and inhibits LPL in peripheral tissues via an endocrine action. The functionality of ANGPTL3 as an LPL inhibitor is dependent on ANGPTL8, which is also produced in the liver and forms a functional complex with ANGPTL3. The primary action of ANGPTL3 in the fed state is probably driven by the strong (insulin-mediated) induction of ANGPTL8 (13).

Abbreviations: ANGPTL3, angiopoietin-like protein 3; ANGPTL8, angiopoietin-like protein 8; GPIHBP1, glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1; HSPG, heparan sulphate proteoglycan; LPL, lipoprotein lipase; TG, triglyceride.

Table 2. Summary of the technology being evaluated (evinacumab).

UK approved name and brand name	INN: Evinacumab Brand name: EVKEEZA®
Mechanism of action	Evinacumab is a recombinant human monoclonal antibody which specifically binds to and inhibits ANGPTL3. ANGPTL3 is a member of the angiopoietin-like protein family that is expressed primarily in the liver and plays a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Evinacumab reduces LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and VLDL remnants clearance upstream of LDL formation through EL-dependent mechanism. This leads to lower circulating levels of LDL-C, TGs, HDL-C, and other lipoproteins and reduces the risk of atherogenic-mediated cardiovascular events and disease
Marketing authorisation/CE mark status	Evinacumab was granted marketing authorisation by the MHRA in August 2022.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Evinacumab is indicated as an adjunct to diet and other LDL-C lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with HoFH.
Method of administration and dosage	The recommended dose of evinacumab is 15 mg/kg administered by intravenous infusion over 60 minutes once monthly (every 4 weeks). There are no dose adjustments required for people who are elderly or have renal or hepatic impairment or for paediatric patients aged 12 to 17 years. Evinacumab should not be used in pregnancy. Treatment with evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders.
Additional tests or investigations	People with HoFH are diagnosed through combinations of genotypical and phenotypical methods. Evinacumab is indicated in all forms of HoFH (true homozygotes, compound homozygotes, and double heterozygotes). No additional diagnostic work up is required.
List price and average cost of a course of treatment	The UK list price for evinacumab is [redacted]. The average cost for a course of treatment would be [redacted] if applying list price and accounting for distribution of patient weights.
Patient access scheme (if applicable)	[redacted]

Abbreviations: ANGPTL3, angiopoietin-like protein 3; EMA, European Medicines Agency; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolaemia; INN, international non-proprietary name; LDL-C, low-density lipoprotein cholesterol; MHRA, Medicines and Healthcare products Regulatory Agency; TGs, triglycerides.

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

Summary

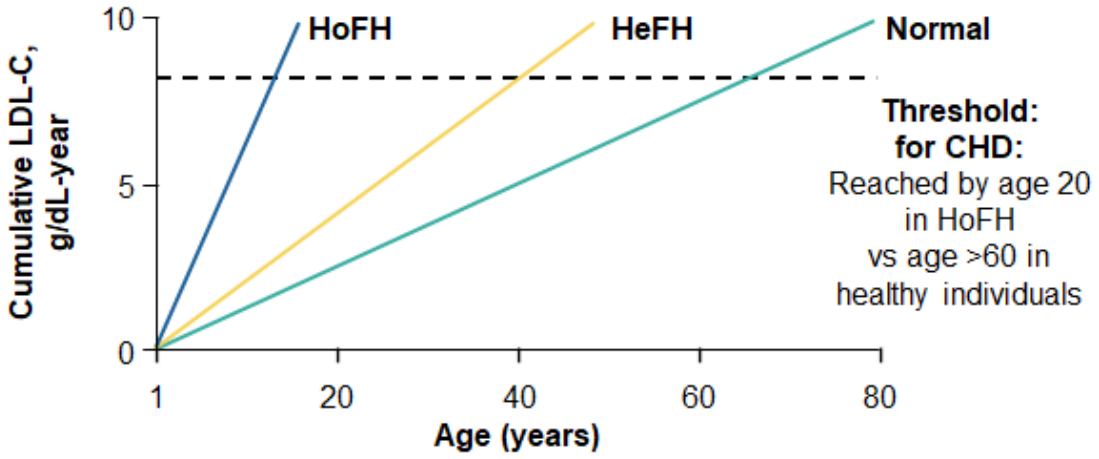
- HoFH is a rare inherited autosomal dominant disorder that results in profoundly elevated levels of circulating LDL-C, other lipoproteins, and TGs. It is an ultra-rare disease estimated to affect about 1 in 670,000 people in the UK, with around 1 new case of HoFH being diagnosed every year.
- HoFH represents a spectrum of genotypically distinct mutations which impact the functionality of LDLRs. Mutations may cause complete or partial loss of function of the LDLR, with the most severe variants being null/null (almost complete loss of function).
- The phenotypic consequence of HoFH is the development of severely elevated levels of circulating LDL-C at a young age. This clinically manifests itself in the development of xanthomas and accelerated atherosclerotic disease. Consequently, this greatly increases the risk of development of CVD with the attendant morbidity and mortality this entails.
- Left untreated, the prognosis for people with HoFH is poor, with the average age of death being around 18 years.
- Treatment of HoFH aims to reduce circulating LDL-C and therefore reduce the incidence of CVD. Treatment is highly individualised because of the range in disease severity and the heterogeneous nature of patient presentation.
- Pharmacological treatments for HoFH include high-intensity statins, ezetimibe, PCSK9 inhibitors (evolocumab), and lomitapide. Non-pharmacological treatments include LDL apheresis and, rarely, liver transplantation.
- A limitation of statins and evolocumab is that they are relatively ineffective in patients with significant loss of LDLR function. Lomitapide is associated with dose-limiting AEs and poor adherence. LDL apheresis can impact on healthcare resource use and opportunity cost, has issues with patient access and geographical inequality, and is an additional burden on the patient and carer.
- Evinacumab has the potential to circumvent many of the issues associated with other treatments and address patients' unmet needs.

B.1.3.1 Aetiology and pathophysiology of the condition

HoFH is an ultra-rare genetic condition associated with elevated LDL-C levels and early development of cardiovascular disease (CVD) (14). HoFH is a form of familial hypercholesterolemia (FH), an autosomal dominant genetic disorder of cholesterol metabolism characterised by profoundly elevated LDL-C and increased risk of premature atherosclerotic cardiovascular (CV) events (14, 15). FH is caused by mutations in genes encoding key proteins involved in the LDLR endocytic and recycling pathways, leading to decreased cellular uptake of LDL, and, consequently, increased plasma LDL-C

concentrations (16). Individuals with HoFH most commonly have two pathogenic mutations in genes affecting LDLR function, one inherited from each parent. This contrasts with people with heterozygous FH (HeFH), who inherit a single mutation from one parent (14). Having mutations in both alleles affecting LDLR function results in much greater elevations in LDL-C. This burden is sufficient enough for people to develop coronary heart disease (CHD) in childhood with increased risk of premature death, compared with healthy people or people with HeFH (16) (Figure 3).

Figure 3. Relationship between cumulative LDL-C exposure and age of CHD development. Adapted from Horton *et al.* (2009) (17).



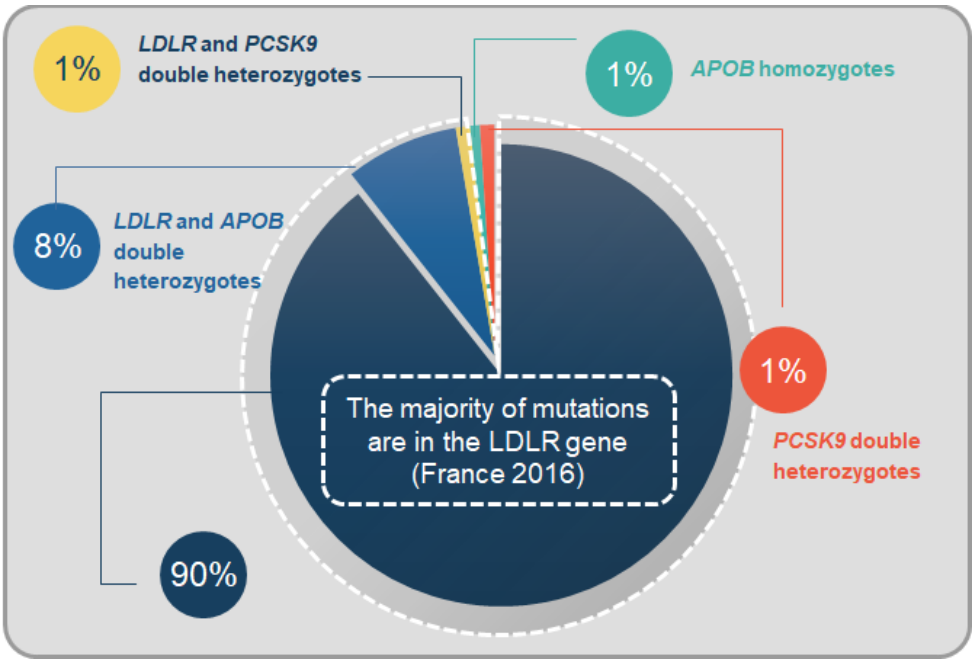
Legend: Cumulative plasma levels of LDL-C were estimated from mean plasma levels of LDL-C for FH homozygotes, FH heterozygotes, and age-adjusted LDL-C levels in normal individuals [calculated from National Health and Nutrition Education Survey III (15, 18)].

Abbreviations: CHD, coronary heart disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

The molecular defects underlying HoFH result from functional mutations in genes (LDLR, apolipoprotein B [ApoB], proprotein convertase subtilisin/kexin type 9 [PCSK9], and low-density adaptor protein 1 [LDLRAP1]) that impair the LDLR pathway. This reduces removal of LDL-C from the blood which leads to atherosclerosis and CV complications (19). In HoFH, about 90% of patients have two mutant alleles of the LDLR gene (20), although several other variations are possible. People with HoFH can be classified into three categories: true homozygotes, compound heterozygotes, and double heterozygotes (2, 20). True homozygotes carry the same mutation on both alleles of the affected gene whereas compound heterozygotes carry a different mutation on each allele of the affected gene. Double heterozygotes carry a mutation on two different genes (

Figure 4).

Figure 4. Expected gene composition in the HoFH population. Adapted from France *et al.* (2016) (20).

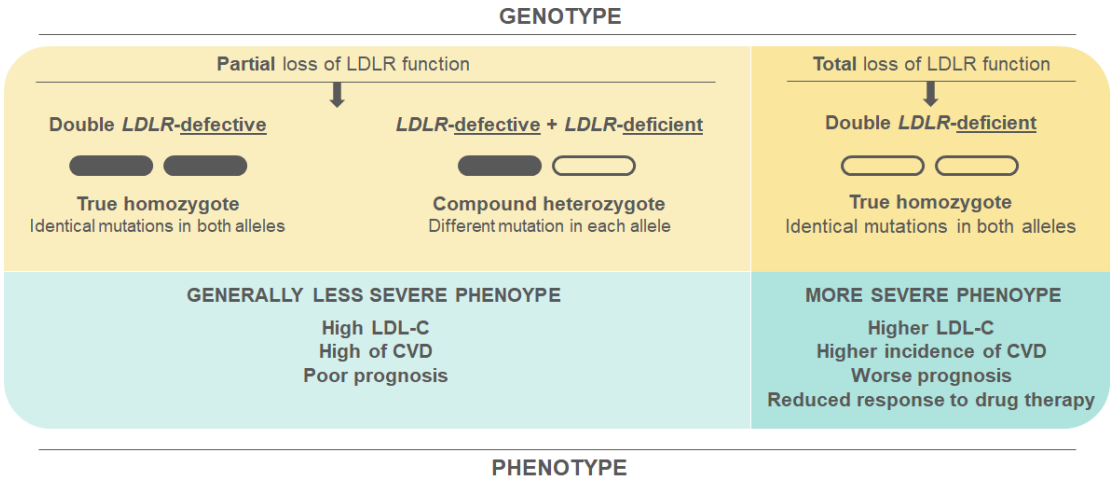


Legend: Prevalence of LDLRAP1 mutations not specified other than being "very rare." HoFH, homozygous familial hypercholesterolemia.

Abbreviations: APOB, apolipoprotein B; LDLR, low-density lipoprotein receptors; PCSK9, proprotein convertase subtilisin/kexin type 9.

HoFH can further be classified based on the extent of the impact of mutations on LDLR functionality. Genotypically, people can be classified as true homozygotes, double heterozygotes, or compound heterozygotes. People who are true homozygotes have the same mutation on the same gene on both alleles, whereas compound heterozygotes carry different mutations on the same gene in each allele, and double heterozygotes have different mutations in different genes of each allele (2, 20). The more severe phenotype, however, is LDLR-deficient ("null-null") status which causes little to no LDL binding and uptake activity. Historically this has been defined as <2% LDLR activity (21). Compound heterozygotes carry a different mutation on each allele of the affected gene, having overall partial loss of LDLR function. A summary of the relationship between LDLR mutations and HoFH phenotype is reported in Figure 5.

Figure 5. LDLR Mutations and Relationship to Homozygous Familial Hypercholesterolemia Phenotype.

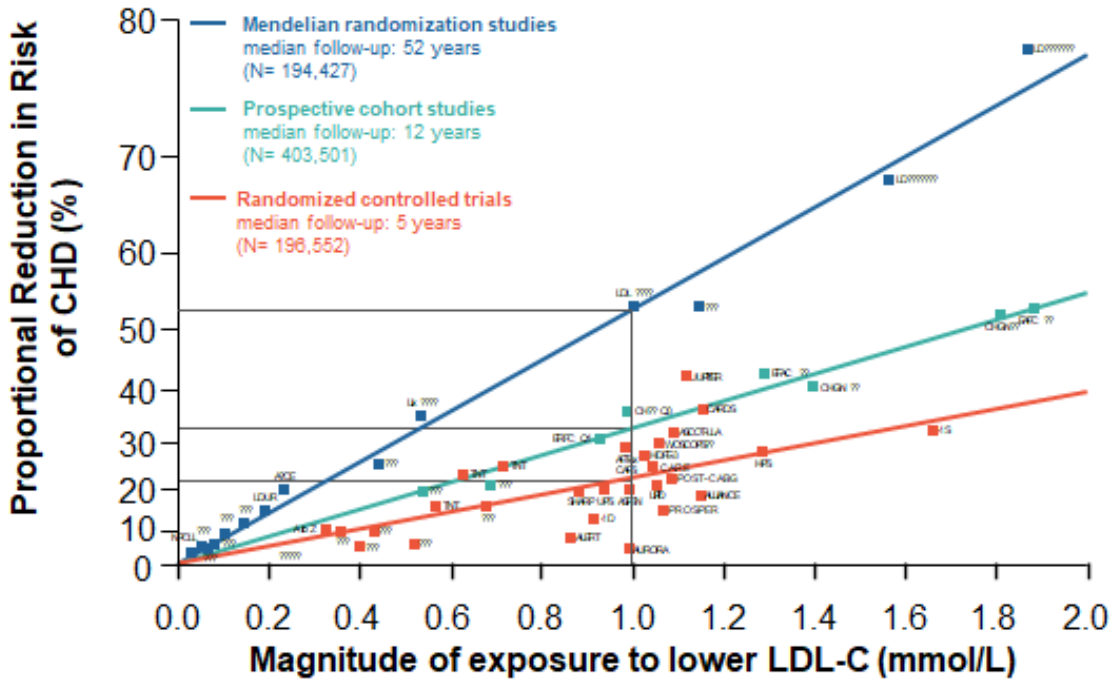


Abbreviations: CVD, cardiovascular disease; LDLR, low-density lipoprotein receptors;

B.1.3.2 Consequence of raised LDL-C

The defining outcome of the genetic defects observed in HoFH is a significant increase in circulating LDL-C levels. LDL-C and other apolipoprotein B (ApoB)-containing lipoproteins (VLDL-C, LDL-C) are known to be atherogenic. Due to the limited HoFH population size, it is challenging to demonstrate direct reductions in CVD or CV events using interventions within the limited timeframe of a clinical trial. However, the association between LDL-C levels and risk of CVD was described as “unequivocal” in the current European Union guidelines on CVD prevention (22). The relationship between LDL-C and CV morbidity and mortality has been recognised for decades and was confirmed by the Cholesterol Treatment Trialists’ (CTT) Collaboration’s individual patient meta-analysis of 174,000 patients enrolled into randomised controlled trials (RCTs) on statins (23). There is now overwhelming evidence supporting the association between high LDL-C levels and increased CVD risk from a variety of sources in addition to RCTs, including genetic, epidemiologic, and Mendelian randomisation studies (24, 25). The causal relationship between exposure to elevated LDL-C and risk of atherosclerotic CVD was further demonstrated by a large meta-analysis conducted by Ference *et al.* (2017) (26). This meta-analysis included more than 200 prospective cohort studies with a total of over 2 million participants with 20 million person-years of follow-up, and 150,000 CV events. The authors reported that any mechanism of lowering plasma LDL-C should reduce the risk of atherosclerotic CV events proportional to the absolute reduction in LDL-C and the cumulative duration of exposure (Figure 6). In otherwise healthy populations, it has been estimated that there is a 22% reduction in the risk of CVD for every 1 mmol/L reduction in LDL-C achieved. In a meta-regression analysis of 49 clinical trials, each 1 mmol/L (38.7 mg/dL) reduction in LDL-C level was associated with a relative risk (RR) of major vascular events of 0.77 (95% CI, 0.71 to 0.84; $P<0.001$) for statins and 0.75 (95% CI, 0.66 to 0.86; $P=0.002$) for established non-statin interventions that act primarily via upregulation of LDLR expression (27).

Figure 6. Log-linear association per unit change in LDL-C and the risk of cardiovascular disease. Adapted from Ference *et al.* (2017) (26).



Abbreviations: CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol. Trial acronyms: AF/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of LEscol in Renal Transplantation; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid Lowering Trial; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus; ASCOT LLA, Anglo Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CARE, Cholesterol and Recurrent Events; CARDS, Collaborative Atorvastatin Diabetes Study; CHGN, Community Health Global Network; 4D Deutsche Diabetes Dialyse Studies; ERFC, Emerging Risk Factors Collaboration; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HOPE, Heart Outcomes Prevention Evaluation Study; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; IMPROVE-IT, Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; LIPS, Lescol Intervention Prevention Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; POST-CABG, Post Coronary Artery Bypass Graft; PROSPER, Pravastatin in elderly individuals at risk of vascular disease; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; SHARP, Study of Heart and Renal Protection; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study.

B.1.3.3 Disease progression and prognosis

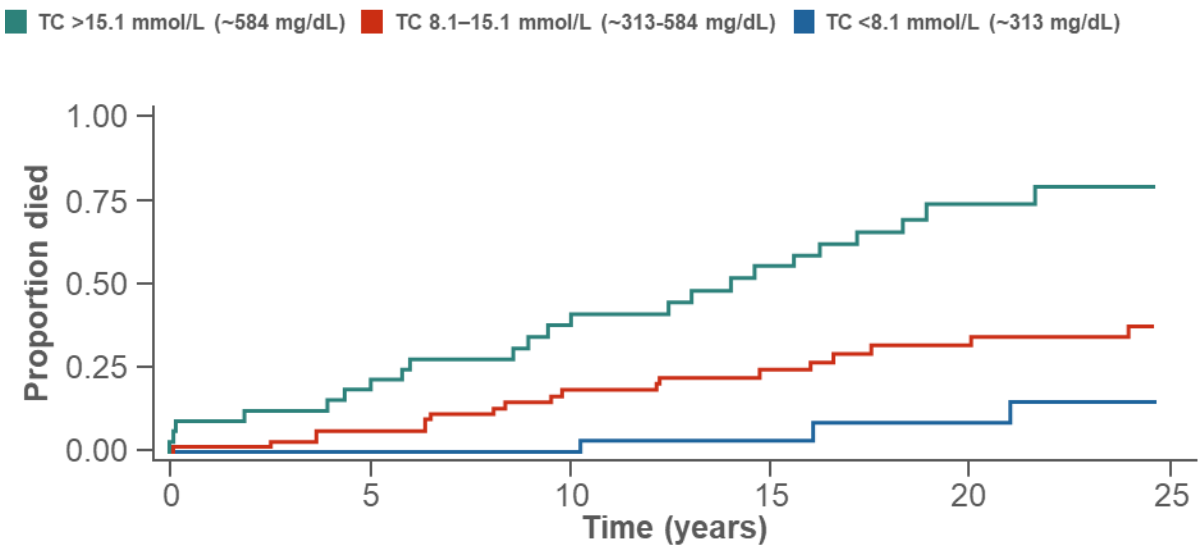
HoFH is a serious, life-long, life-threatening disease with a generally poor prognosis, despite the current standard of care. As a consequence of chronic exposure to dangerously elevated LDL-C levels, patients with HoFH are at increased risk of early CV events (including myocardial infarction [MI], stroke, and heart failure) compared with the general population. This can lead to sudden cardiac death in childhood or adolescence (2, 14, 28-32). Carotid arterial wall atherosclerosis progression has been shown to be evident from age 12 years onwards (33-35), with LDL-C typically accumulating to a threshold sufficient for development of CHD by the age of 20 years. In a healthy individual, this would typically be reached above the age of 60 (17). Furthermore, in a study that included 39 patients with HoFH (n=22, aged ≤16 years), coronary angiography showed evidence of early mild coronary atherosclerosis in children as young as 7 years (36). Globally, the median age of diagnosis of HoFH has been reported as 12 years (37). Left untreated, the average age of death in people with HoFH has been reported as 18 years (38).

Patients with HoFH are at a 100-fold elevated MI risk versus those without the condition (39). Other associated lipid/lipoprotein defects [e.g., elevated lipoprotein(a)], which also increase CV risk, may accompany LDL-C elevations (40). The prognosis is partly dependent on the form of HoFH an individual has, with particularly worse outcomes if they have the LDLR-deficient genotype (14).

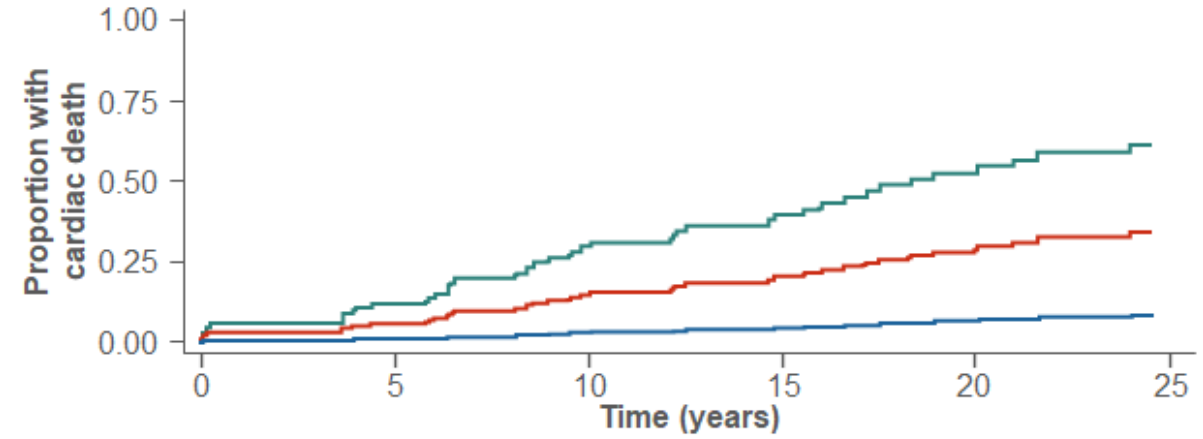
Reduction of circulating LDL-C levels, by any means, reduces CV mediated morbidity and mortality (26), an outcome demonstrated in a HoFH study by Thompson *et al.* (2020) (41). The authors conducted a pooled analysis of two retrospective surveys involving HoFH patients in South Africa (n=149) and the UK (n=44) on lipid-lowering therapy (LLT), reporting that higher serum total cholesterol (TC) levels were associated with worse clinical outcomes. Kaplan-Meier survival curves showed statistically significant increased risk of all-cause mortality and CV death associated with higher cholesterol levels (Figure 7) (41). These findings highlight the importance of achieving as close to target LDL-C goals as possible on LLT to improve CV-related survival in patients with HoFH.

Figure 7. Increasing risk of (A) all-cause mortality and (B) cardiovascular death with higher cholesterol levels (on lipid-lowering treatment).

(A)



(B)



Abbreviations: TC, total cholesterol.

B.1.3.4 Patient burden and health-related quality of life

People diagnosed with HoFH are subject to a significant clinical burden which impacts on their health-related quality of life (HRQoL) relating to the physical and psychological manifestations of the disease, cardiovascular morbidity, and negative consequences associated with treatment. A systematic review and meta-analysis that investigated the association between HoFH and HRQoL concluded that patients suffer disease-related impairments in quality of life (42). In a pooled analysis of Short Form-36 (SF-36) outcomes, patients with HoFH reported significantly poorer HRQoL in multiple dimensions relative to the general population, including physical functioning, role limitation, social functioning,

bodily pain, and general health (43, 44). Patients have also been found to have increased risk of anxiety disorders and depression based on the Hospital Anxiety and Depression Scale (HADS) score, with cardiovascular involvement also resulting in higher anxiety (43). Other findings have shown adverse impacts on self-perception including feelings of devaluation and stigmatisation as well as negative impacts on educational attainment and employment (45-47).

Several studies have highlighted the significant treatment-related burden (Section B.1.3.7 Pharmacological management with current drug treatment and, in particular, the negative impact of lipoprotein apheresis, impacting physical, temporal, and travel-related commitments (43, 45, 48, 49) (Section B.1.3.8 Non-pharmacological treatments). HRQoL has also been demonstrated to be reduced following serious CV events, such as MI (50) and stroke (51), the risk of which are greatly elevated in patients with HoFH.

B.1.3.5 Prevalence of HoFH

HoFH may be termed an ultra-rare or ultra-orphan disease, based on the typical definition of a prevalence of <20 per million (2, 16). Actual prevalence estimates can vary based on several factors related to the data collection method used (e.g., phenotypically, genotypic profiling, or extrapolation methods based on prevalence of HeFH) (52). In 2019, the Task Force for the management of dyslipidaemias of the European Society of Cardiology and the EAS reported a range of prevalence figures between 1 in 160,000 and 1 in 320,000 individuals (17).

In the UK, the estimated prevalence of HoFH, based on an assumption of 1 in 500 people having HeFH, is 1 in 1,000,000 (20). Based on actual patient numbers being treated in major apheresis centres, it has been estimated that the prevalence of HoFH may be 1 in 670,000 adults in England, with around 1 new case of HoFH being diagnosed every year (3). However, it is thought that a lack of awareness of HoFH among physicians, as well as lack of neonatal screening, contributes to the condition being underdiagnosed (53). Screening for FH is not currently recommended in the UK as part of the Child screening programme (54).

B.1.3.6 Patient management pathways

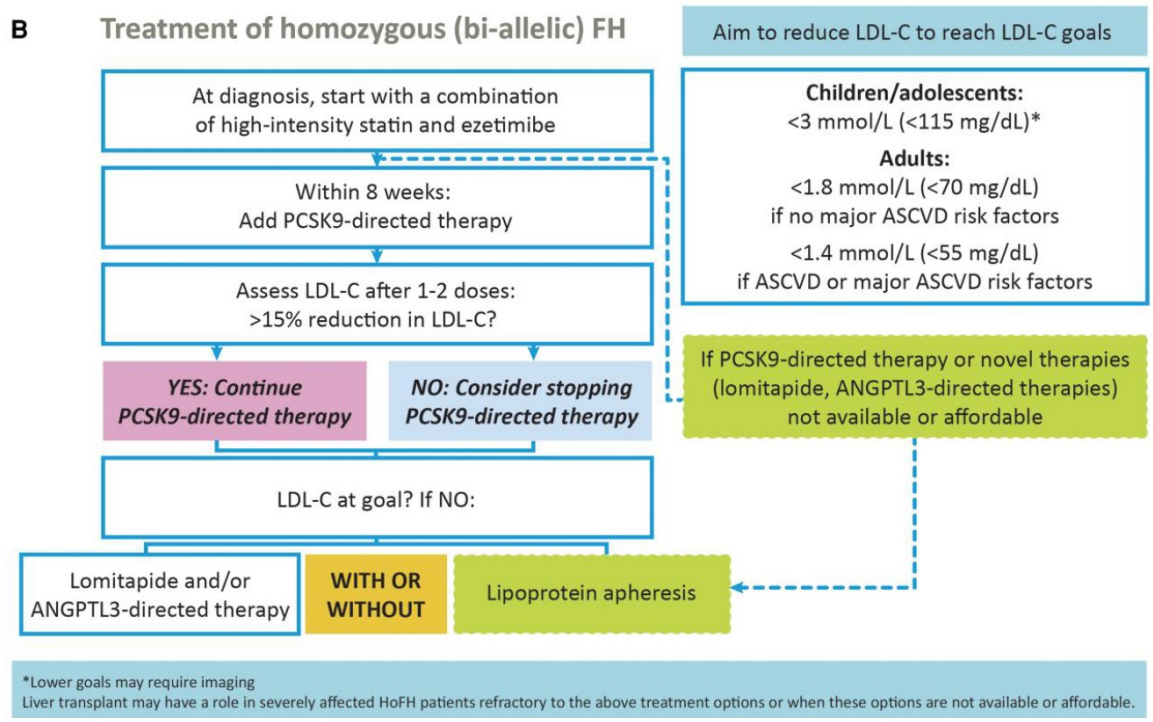
HoFH is an ultra-rare disease with a heterogeneous presentation, which means management needs to be individualised to patient needs. As such, there are no specific NICE clinical guidelines on the management of the condition, treatment algorithms, nor technology appraisals covering treatment of this disease specifically. There are NICE clinical guidelines on *Familial hypercholesterolaemia: identification and management* (55) that provides advice on the diagnosis and ongoing management of HoFH from a process-driven perspective. The principal message advised by NICE is that people with confirmed HoFH should be managed under a multi-disciplinary team (MDT) at a specialist centre (further information is reported in Table 3).

In the UK, there is a consensus statement from the *HEART UK Medical Scientific and Research Committee* which discusses best practice and treatment options for HoFH, prior to the availability of evinacumab (20). The most widely recognised guidance on the management of HoFH is the European Atherosclerosis Society (EAS) consensus guidelines, published in 2014, after the introduction of lomitapide and PCSK9 inhibitors, but prior to the

development of evinacumab (2). The International Atherosclerosis Society (56) and the American Heart Association guidelines (16) placed treatment with lomitapide after PCSK9 inhibitors, at the same treatment stage as LDL apheresis, which could be used alone or in combination with available pharmacological treatments. However, these guidelines were published before evinacumab was an available treatment option.

New EAS consensus guidelines published in May 2023 show both evinacumab and lomitapide as a third line treatment option in developed countries (according to availability and affordability) (4). Evinacumab or lomitapide would be used before LDL apheresis, which would remain as an adjunctive option only for patients who could not achieve targets despite maximal available pharmacological therapy. This treatment order has been confirmed by a recent review (57). The treatment algorithm pathways are reported in Figure 8. Thus, it can be seen that evinacumab is an alternative to lomitapide, placed at the same point in the patient pathway, and as such is logically a comparator treatment. Given the very recent publication, these guidelines are not yet adopted in clinical practice in England. For this reason, in the economic evaluation, patient pathways are consistent with the EAS 2014 consensus statement (2), as they more accurately represent current practice in the UK (as of May 2023).

Figure 8. EAS consensus guidelines (2023) (4).



Abbreviations: ANGPTL3, angiopoietin-like protein 3; ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

The following is a summary of the available management strategies for people with HoFH, although as discussed, in practice treatment will be highly individualised. This summary is

derived from currently available guidelines and reflect current medical opinion and practice (Table 3).

Table 3. NICE guidance relevant to HoFH (2008, updated 2019) (55).

Diagnosis	Adults with LDL-C >13 mmol/L
	Children/young people with LDL-C >11 mmol/L (also see section on diagnosis) LDL-C should be measured before the age of 5 years or at the earliest opportunity thereafter in children at risk of HoFH because of two affected parents or because of the presence of clinical signs (e.g., xanthomata)
Treatment	In children and young people with HoFH, LDL-C may be lowered by lipid-modifying drug therapy; this should be considered before lipoprotein apheresis
	Liver transplantation should be considered as an option for patients with HoFH after treatment with lipid-modifying drug therapy and lipoprotein apheresis
Management	Patients with HoFH should be offered referral to a specialist centre Upon diagnosis, patients with HoFH should a referral for an evaluation of CHD risk
	Prescribing of drug therapy for adults with HoFH should be undertaken within a specialist centre
	Shared care arrangements to include expertise in cardiology and obstetrics are essential for women with HoFH who are considering pregnancy or are pregnant; this should include an assessment of CHD risk, particularly to exclude aortic stenosis

Abbreviations: CHD, coronary heart disease; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low density lipoprotein cholesterol.

B.1.3.6.1 Diagnosis

In contrast to HeFH, HoFH often presents early in life with physical signs and symptoms of the disorder. Common physical examination findings include cutaneous or tuberous xanthomas, tendon xanthomas (with interdigital xanthomas between the thumb and index finger being pathognomonic), xanthelasma, and arcus corneae (58). The clinical diagnosis of HoFH is a two-step process that firstly involves diagnosis of FH (for example, via the Dutch Lipid Clinic Network criteria, MEDPED, or Simon Broome Register methods), followed by differentiating HoFH from HeFH (16). These diagnostic tools assess LDL-C levels, physical findings (e.g., tendon xanthomas), family history of FH or premature CVD, and genetic testing (59). As clinical signs alone may fail to diagnose HoFH, genetic testing is recommended as standard of care for patients with definite or probable FH, as well as for "at-risk" relatives. Detailed criteria for genetic testing have been established by an international expert panel convened by the Familial Hypercholesterolemia Foundation (60). In the UK, the following diagnostic criteria are recommended in accordance with the European Atherosclerosis Society (EAS) (20):

- Presence of 2 disease causing alleles affecting introns and exons of the LDLR, ApoB, PCSK9, and LDLRAP1 gene loci *OR*

- LDL-C >11.0 mmol/L in children with tendon or cutaneous xanthomata before the age of 10 years, or 13.0 mmol/L in adults with clinically obvious tendon or cutaneous xanthomata. But because of the now recognised genetic and clinical heterogeneity of HoFH, lower LDL-C does not exclude HoFH. Genetic diagnosis, supplementary to clinical assessment including cholesterol, is preferred *OR*
- Qualifying cholesterol level and both parents with genetically confirmed HeFH

These criteria have been iteratively developed in the latest EAS consensus guidelines (2023) (4). These guidelines recommend an untreated LDL-C level of 10 mmol/L should trigger further evaluation including possible genomic investigation.

Following diagnosis, a full clinical management plan will be developed with appropriate diagnostic work up to assess the risk of the underlying risk of CVD and to initiate the management of comorbidities. The aims of treatment are to reduce lipoprotein to target levels, using these as a proxy or surrogate for the clinical efficacy of interventions used. For LDL-C, a “lower is better” approach is taken, with the “sooner the better” being another relevant maxim, reflecting the need for initiation of treatment in individuals as young as possible in order to lower their cumulative exposure. Lipoprotein treatment targets should match those that are used for HeFH (Table 4) (20).

The current pharmacological treatment options for HoFH in the UK are statins (usually high-intensity), ezetimibe, PCSK9 inhibitors (evolocumab), and lomitapide (Section B.1.3.7 Pharmacological management). In a majority of patients with HoFH, these treatments are used in combination to elicit the maximal response on LDL-C lowering. The principal non-pharmacological treatment used in patients with HoFH is LDL apheresis. Another (seldom used) option is liver transplantation (61) (Section B.1.3.8 Non-pharmacological treatments). However, all interventions have significant limitations in people with HoFH, both when used individually or collectively.

Treatment of HoFH is typically highly individualised depending on the patient’s age, genetic (underlying mutations) and phenotypic diagnosis, and the presence and severity of CVD. Treatment is additive, meaning most patients are receiving multiple combinations of drugs and/or LDL apheresis. Treatments for HoFH have independent mechanisms of action targeting different biochemical pathways and some drugs may demonstrate synergistic efficacy (62). High-intensity statins are widely used as a first-line therapy, often combined with ezetimibe and other adjunctive LDL drugs. If these are insufficient to achieve an adequate response in LDL-C reduction (e.g., to meet treatment targets of reducing LDL-C by 50%), as is nearly always the case, second-line treatments such as subcutaneous evolocumab or LDL apheresis may be used. However, these are not suitable for all people. For instance, evolocumab is ineffective in people with mutations affecting the PCSK9 gene, or people with null/null LDLR mutations. Therefore, usually addition of these is still inadequate to achieve an optimal response (2). For these patients, lomitapide may be considered. Evinacumab would be an alternative to lomitapide at this stage. A schematic pathway for the current treatment of HoFH in the UK, and the anticipated place of evinacumab within this, is reported in

Figure 9.

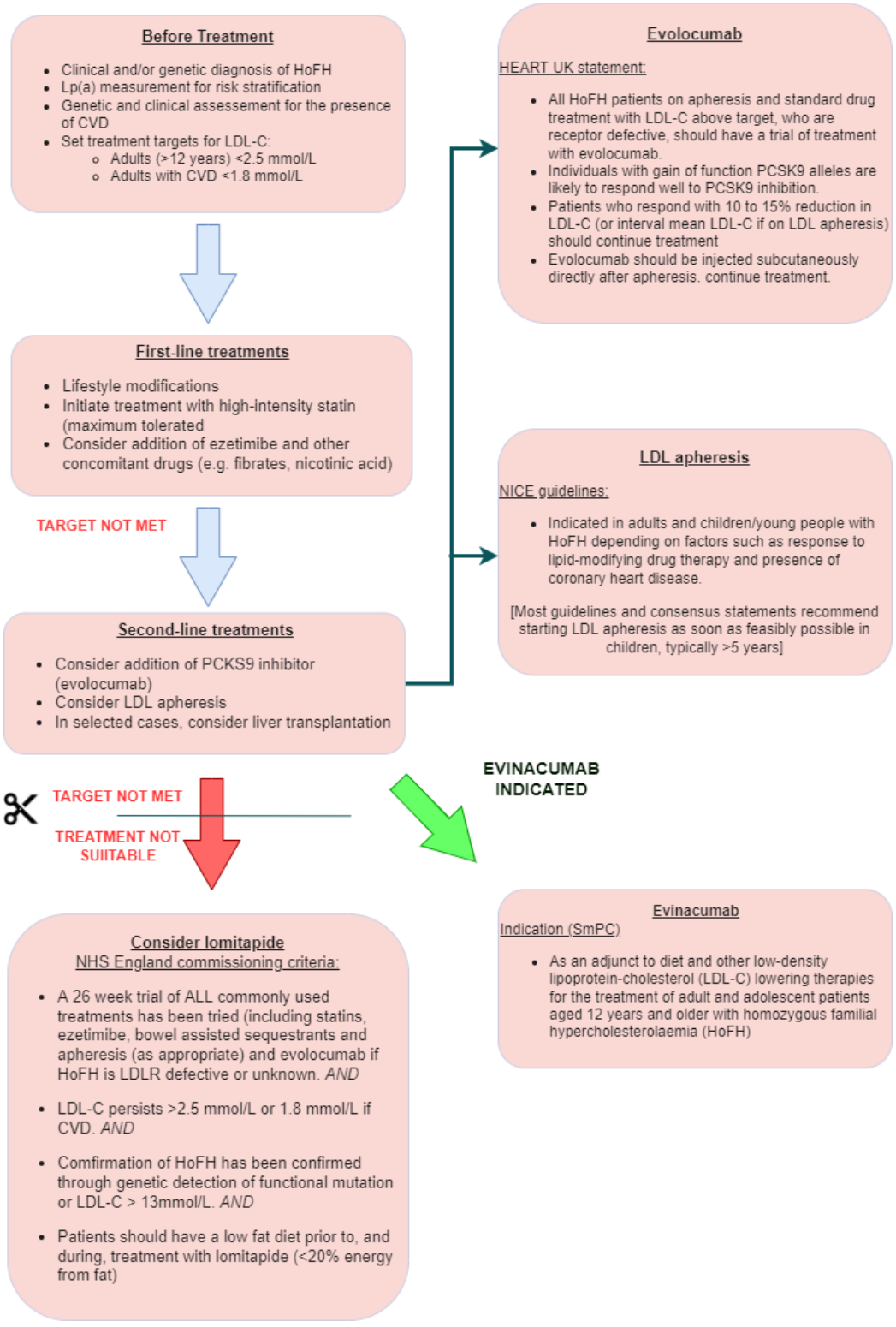
Table 4. Circulating cholesterol targets in people with HoFH.

Group	LDL-C (mmol/L)	Non-HDL-C (mmol/L)
Adults (>18 years)	<2.5	<3.3
Adults with CVD	<1.8	<2.6
Children	<3.5	<4.3

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Targets apply to the interval mean. For patients on apheresis or techniques lowering HDL-C, only LDL-C should be used.

Figure 9. UK treatment algorithm for management of HoFH (derived from several sources).



Abbreviations: CVD, cardiovascular disease; EAS, European Atherosclerosis Society; FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; PCSK9; proprotein convertase subtilisin/kexin type 9; SmPC, summary of product characteristics.

Derived from guidelines and consensus statements including NICE (55), NHS England (3), HEART UK (63) and EAS (2).

B.1.3.7 Pharmacological management

B.1.3.7.1 Statins

Approved statins used for HoFH include atorvastatin, rosuvastatin, and simvastatin (64-67). All patients should be offered maximum doses of atorvastatin or rosuvastatin combined with ezetimibe, with other statins reserved for people who are intolerant of these regimens (20). Statins have a well-established safety profile, with a low incidence of adverse events (AEs) and can be used in paediatric populations. However, dose-related AEs can be a concern, with real-world studies having reported statin intolerance in up to 30% of all treated patients (68). Statins have the potential for drug-drug interactions, which can limit the tolerability of combination therapy (64-67, 69-72).

However, a limitation of statins is they reduce LDL-C in patients with HoFH to a materially lesser extent than in other indicated populations (14). This difference may be due to the LDLR-mediated mechanism of action with statins, which achieve LDL-C reduction in part through an increase in the expression of LDLRs. Thus, patients without functional LDLRs (i.e., receptor-deficient patients) have a wide range of responses to treatment, with LDL-C changes between -48% and 0% reported, and an average of approximately -15% (73, 74). In contrast, receptor-defective HoFH patients, who retain up to 30% of LDLR activity, have a range of LDL-C change -42% to -5%, with an average of -26% (73, 74). In comparison, statins used in other patients with hypercholesterolemia are associated with changes in LDL-C levels of -60% to -40% (2, 14).

B1.3.7.2 Ezetimibe

Ezetimibe is approved in combination with a statin (atorvastatin or simvastatin) as an adjunctive therapy to diet for use in patients with HoFH. Ezetimibe has demonstrated efficacy in patients with HoFH (75) and has a well-established safety profile, with few associated with infrequent gastrointestinal (GI) or musculoskeletal AEs (75). It has no specific limitations in people with HoFH, although its efficacy is modest and generally limited to around 15 to 20% when used as an adjunct to a statin (75, 76).

B.1.3.7.3 PCSK9 inhibitors

Evolocumab, a PCSK9 inhibitor, is approved as an adjunct to diet and other LDL-C-lowering therapies in patients with HoFH who require additional LDL-C reduction (70). Similar to statins, PCSK9 inhibitors have a mechanism of action reliant on LDLR function, and evolocumab appears to be only modestly effective in patients with HoFH, achieving changes between -31% and -21% (77, 78). Evolocumab is almost completely ineffective in patients with receptor-deficient mutations (78), who comprise approximately between 9% to 25% of patients with HoFH (5, 20, 79, 80). These differences are attributed to variable LDLR expression (16). Therefore, the efficacy of evolocumab is dependent on the mutation type. In trials of evolocumab in HoFH, LDL-C change was approximately -25% in receptor-defective patients and 0% in receptor-deficient patients (78, 81, 82).

Another PCSK9 inhibitor, alirocumab, is not specifically licensed for the treatment of HoFH in the UK (83). Based on data reported in the ODYSSEY trial, it has demonstrated an efficacy of -35.6% in reducing LDL-C (-26.9% alirocumab vs. 8.6% for placebo, $p < 0.0001$) (84).

B.1.3.7.4 Lomitapide

Lomitapide, a microsomal triglyceride transport protein (MTP) inhibitor, is approved as an adjunct to other lipid-lowering medicinal products with or without lipoprotein apheresis in adults with HoFH (6, 85). Lomitapide reduced LDL-C by approximately 50% in a single-arm pivotal clinical trial, based on per protocol population (PP) analysis (n=23) using a median dose of 40 mg/day (78). Data from the Lomitapide Observational Worldwide Evaluation Registry (LOWER) (86) reported a change in LDL-C of -45.3% at 6 months in patients taking the drug; however results from this real-world study were potentially confounded by a large proportion of people discontinuing treatment as well as requiring dose reductions. For comparison, there was a -33.9% change at the same timepoint in the overall LOWER cohort, of which two thirds of the participants (42/63) were *not* receiving lomitapide .In the pivotal trial, 93% (27/29) of patients treated with lomitapide reported GI AEs during the efficacy phase, with diarrhoea (79%) and nausea (65%) being the most common AEs (87). Lomitapide is associated with significant dose-limiting safety issues including high rates of GI side effects and hepatic abnormalities, such as hepatic steatosis and elevated liver enzymes (87). As a result, some patients treated with lomitapide may be unable to achieve maximum lipid-lowering effect (88).

Lomitapide has a black box warning in the US and a Risk Evaluation and Mitigation Strategy program in place (14, 85). Dietary modification and clinical monitoring are required to limit the risk of fatty liver (steatohepatitis), which remains a major concern (89). In the UK, lomitapide is listed as a ‘black triangle drug’ with special warnings and precautions for use. These precautions are due to concerns with liver enzyme abnormalities and liver monitoring, monitoring of liver function tests, dose modifications based on elevated aminotransferases, and the assessment of the risk of hepatic steatosis and progressive liver disease, which may require imaging for hepatic tissue elasticity (e.g., Fibroscan™, acoustic radiation force impulse [ARFI], or magnetic resonance [MR] elastography) (90). Additionally, lomitapide is metabolised through CYP3A4 and is sensitive to inhibitors or inducers of this isozyme. There is the potential for clinically important drug-drug interactions, including with the concomitant use of statins (68).

Lomitapide, although indicated as an adjunct to a low-fat diet, requires additional dietary restrictions. Guidance from the Summary of Medicinal Product Characteristics (SmPC) stipulates that patients should consume a diet supplying <20% of energy from fat prior to treatment initiation, and should continue this diet throughout treatment with the addition of dietary counselling (91). It is further recommended that patients should take dietary supplements that provide 400 IU vitamin E and approximately 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA), and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment (90).

Stopping criteria published by NICE stipulates that treatment with lomitapide should be stopped if LDL-C levels do not drop by 20% of pre-lomitapide levels and/or if the patient is unwilling or unable to adhere to a low fat diet (<20% energy from fat) (3). The potential

hepatotoxicity of lomitapide, as well as poor adherence to both lomitapide dose titration and dietary restrictions, has meant that many UK specialists use lomitapide cautiously, especially at higher doses (91).

B.1.3.8 Non-pharmacological treatments

The principal non-pharmacological treatment strategies are diet and lifestyle modifications, LDL apheresis, and liver transplantation.

B.1.3.8.1 Lifestyle interventions

Lifestyle intervention should be encouraged in all patients but does not significantly reduce LDL-C (2). Recommended measures include a low-saturated fat and low-cholesterol diet, maintenance of healthy weight, physical activity, smoking cessation, and alcohol restriction. Additionally, effective high-intensity management of other diseases which impact on CVD risk, such as hypertension and diabetes, should be undertaken.

B.1.3.8.2 LDL apheresis

Lipoprotein apheresis is an invasive procedure that consists of extracorporeal therapy in which the blood of a patient is removed from the body and passed through a filtration device, whereupon undesirable lipoprotein elements present in the blood are eliminated (92). Lipoprotein apheresis has been shown to acutely change LDL-C levels by -62% to -69% compared with pre-treatment levels in patients with HoFH (93). However, due to rapid rebound effects, the interval mean is the most appropriate outcome to determine LDL-C lowering efficacy when comparing this with other forms of LLT (94, 95). Typically, changes in LDL-C of between -40% and -30% are achieved using this metric (96)

LDL apheresis is a highly sophisticated technique that must be performed weekly or biweekly in an appropriate clinical setting and requires specialised training of healthcare professionals (2, 96-98). Lipoprotein apheresis has a variety of indications; in the context of HoFH, the goal of lipoprotein apheresis is to reduce levels of potentially harmful cholesterol molecules, including LDL-C (97).

Lipoprotein apheresis is frequently required in addition to pharmacologic treatment to meet LDL-C goals in the management of patients with HoFH (99). The decision to treat with lipoprotein apheresis must balance the potential clinical benefit and severity of the disease with the frequency of treatment required, affordability, and patient choice. Depending on disease severity, the patient may need lengthy weekly or biweekly treatments of 2 to 3 hours each; the high frequency of treatment also provides tight control and ensures regular monitoring of medical issues (100). Adverse events (e.g., hypotension, abdominal pain, nausea, hypocalcaemia, iron-deficiency anaemia, and allergic reactions) and problems at the venous access site with lipoprotein apheresis may limit utility of apheresis (2).

LDL apheresis has several limitations in the treatment of HoFH. It is an invasive procedure that impacts patient and family quality of life (95, 96, 100) and can be cumbersome to administer, requiring long-term maintenance of vascular access and carrying a risk of infection. Due to the transient acute effect of lipoprotein apheresis, most patients who undergo the procedure do not maintain the recommended LDL-C levels necessary in

reducing the residual risk. As LDL-C levels return to near-baseline levels within 1 to 2 weeks, lipoprotein apheresis fails to provide HoFH patients with a sustained clinical benefit and must be performed frequently to maintain LDL-C reduction (100).

Patient adherence to lipoprotein apheresis is often suboptimal because of the various drawbacks of treatment (43, 101). Common reasons for patients discontinuing lipoprotein apheresis include treatment refusal, inability to tolerate treatment, inability to obtain reliable vascular access, and moving away from a treatment centre (101). Treatment centres offering lipoprotein apheresis are not uniformly available (102), and the nearest centre may be distant from a patient's home, further contributing to adherence and persistence challenges. In England, there is only a limited number of centres available that offer LDL apheresis, and there are none in Scotland or Northern Ireland, leaving large areas without a local service (20). Barriers to implementation and a lack of available apheresis centres (103) results in few patients overall receiving adequate treatment (96).

B.1.3.8.3 Liver transplantation

Liver transplantation restores hepatic LDLR functionality by replacing dysfunctional LDLRs in the liver to restore hepatic cholesterol metabolism (61). Liver transplantation results in rapid and sustained change in LDL-C levels by approximately -80% and leads to stabilisation or regression of vascular disease and regression of skin xanthomas (104). When performed early, liver transplantation may prevent the development of severe atherosclerosis and aortic valve stenosis (61). Whilst liver transplantation is recommended as a last-line option by NICE (see Table 3) (105), it is regarded as a treatment of last resort and the procedure is very rarely performed for people with HoFH because their need for a liver transplant is not prioritised above that of a patient with hepatic failure (3). Additionally, there is a shortage of suitable donor organs and high rate of complications with this procedure.

A summary of the limitations of the available treatments (pharmacological and non-pharmacological) are reported in Table 5.

Table 5. Summary of current treatment for HoFH.

Treatment	Statins	Ezetimibe	PCSK9 inhibitors	Lomitapide	LDL apheresis
Background	Introduced: simvastatin, atorvastatin, and rosuvastatin indicated for HoFH Type: Small molecule pharmaceutical	Introduced: as adjunctive treatment with statin Type: Small molecule pharmaceutical	Introduced: circa 2015 Type: Monoclonal antibody family (evolocumab and alirocumab)	Introduced: 2012 (FDA approval) Type: Small molecule pharmaceutical	Introduced: circa 1980s Type: MedTech device
Mechanism of action	Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, LDLR dependent: Yes	Reduction of uptake of lipids from GI tract LDLR dependent: partly	Inhibition of PCSK9 protein leading to upregulation of LDLR LDLR dependent: Yes	Inhibition of MTP, direct reduction in hepatic LDL-C production LDLR dependent: No	Physical separation and removal of LDL-C from blood LDLR dependent: No
Place in therapy*	First-line Children aged 8 to 10 years	Second line as adjunct to statin treatment Children aged ≥6 years	Third-line after high-intensity statins plus ezetimibe Children ≥10 years	Third-line after maximal pharmacotherapy and/or LDL apheresis Adults ≥18 years	Used additionally to pharmacotherapy to achieve LDL-C targets Adults and children
Evidence base †	Low quality (in HoFH) High risk of bias, high uncertainty	Moderate quality Some concerns about	High quality Low risk of bias, low uncertainty	Low quality High risk of bias, high uncertainty	Very low quality High risk of bias, high uncertainty
Efficacy (LDL-C change) ‡	<-20% (rosuvastatin and atorvastatin) (106)	-14% (additional to statin) (75)	-30.9% evolocumab (78) -35.6% alirocumab (107)	-40.1% (ITT) (108) -50.0% (PP) (87) †	Around -40% (95)

Treatment	Statins	Ezetimibe	PCSK9 inhibitors	Lomitapide	LDL apheresis
Safety profile	Generally well tolerated. Some dose-related AEs (liver, myopathy)	Generally well tolerated. Infrequent GI or musculoskeletal effects.	No organ system toxicity Hypersensitivity reactions	Hepatotoxicity (lipid accumulation). Elevated LFTs GI related adverse events. Poorly tolerated, low adherence, high discontinuation.	No organ system toxicity Repeated venous access needed, risk of infection
Limitations and/or barriers to access	Ineffective in null-null HoFH	Possibly reduced effectiveness in null-null HoFH	Ineffective in null-null HoFH	Poor adherence to treatment. Frequent LFTs and liver imaging needed	Requires biweekly specialist care Geographical inequality

Abbreviations: Adverse event; ANGPTL3, angiopoietin-like 3; EAS, European Atherosclerosis Society; FDA, Food and Drug Agency; GI, gastrointestinal; HoFH, homozygous hypercholesterolaemia; IV, intravenous; ITT, intention to treat; LDL-C, low density lipoprotein cholesterol; LDLR, low density lipoprotein receptor; LFT, liver function test; MTP, microsomal triglyceride transfer protein; PCSK9, Proprotein convertase subtilisin/kexin type 9; PP, per protocol.

* According to EAS consensus guidelines (2).

† Appraisal of pivotal trial using Cochrane Risk of Bias tool 2 (109) (PCSK9 inhibitors, evinacumab) or Newcastle-Ottawa critical appraisal tool (110) (LDL apheresis, lomitapide. These studies are also subject to confounding).

‡ Data taken from pivotal trial where applicable (no suitable data retrieved for LDL apheresis). Relative change in LDL-C compared with placebo using ITT analysis (PCSK9 inhibitors and evinacumab). Relative reduction in LDL-C compared with baseline using PP analysis (lomitapide, ITT estimate -40% change).

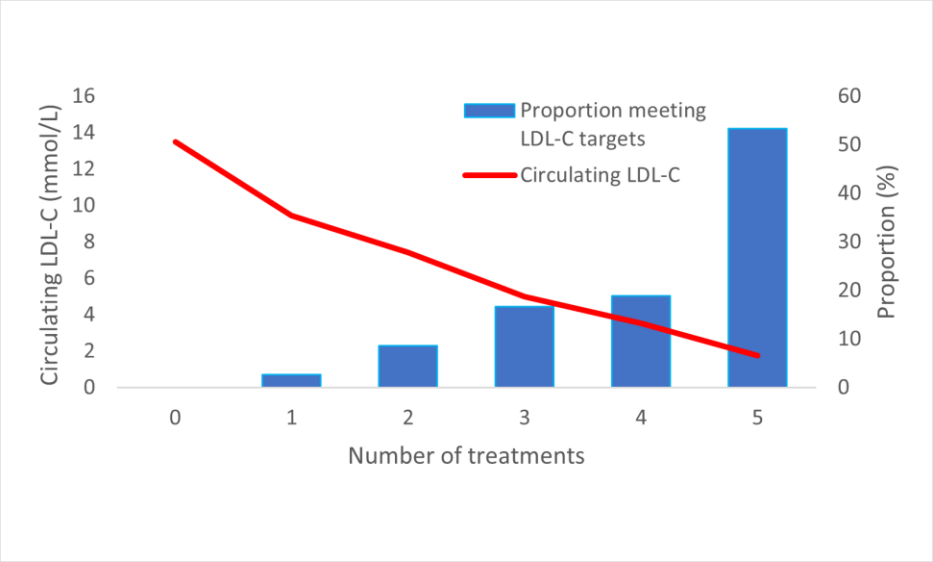
B.1.3.9 Unmet needs

Despite the number of treatments available, there remains considerable unmet need in the HoFH population, resulting in physical signs of hypercholesterolaemia and reduced HRQoL (Section B.1.3.4 Patient burden and health-related quality of life. Most importantly, accelerated atherogenic mediated CVD results in severe clinical manifestations as early as the first decade of life (33, 34, 36, 111). If left untreated, patients can be exposed to >500mg/dL of LDL-C before the age of just 10 years (1, 112). In a longitudinal evaluation of cardiovascular disease in patients with HoFH (n=22, aged ≤16 years), coronary angiography showed evidence of early mild coronary atherosclerosis in children as young as 7 years (1, 36, 111). Further studies have also demonstrated carotid arterial wall atherosclerosis progression from the age of 12 years (33-35), with LDL-C typically accumulating to a threshold sufficient for development of CHD by the age of 20 years. In a healthy individual, this would typically be reached above the age of 60 years (17). Ultimately, this elevated risk and incidence of CV events drives a significant decrease in life expectancy compared with the general population (113, 114), with complications leading to sudden cardiac death in childhood or adolescence (2, 14, 28-32).

Whilst some people with HoFH respond well to the use of statins, ezetimibe, and evolocumab, people with this disease exhibit a spectrum of genetic variation, and these drugs are not sufficient to achieve optimal LDL-C levels. This usually means using multiple concomitant therapies, as illustrated in Figure 10. Even when maximal treatment is used (5 concomitant methods of LLT), only 53.3% of people achieve their lipid targets (57).This is particularly problematic for those who have the most severe mutations (null/null or negative/negative).

For people who have no or only residual LDLR activity, the additional use of lomitapide and LDL apheresis are the only options to achieve a meaningful reduction in LDL-C, either alone or in combination. However, both these interventions have significant practical drawbacks as well as being associated with significant AEs (**Error! Reference source not found.**), which can negatively impact the efficacy as well as patient adherence. In reality, the majority of HoFH patients do not achieve accepted recommended LDL-C targets despite treatment with various classes LLT (2), and thus remain at high risk of CVD.

Figure 10. Cumulative effect of treatments on LDL-C levels and target achievement.



Abbreviations: LDL-C, low-density lipoprotein cholesterol.

Data derived from Tromp *et al.* (2022) (57). The graph shows that as the number of concomitant background treatments are increased, the circulating levels of LDL-C fall and the proportion of patients hitting targets* increases. However, even when 5 treatments are used, only around half of patients achieve their targets.

* LDL cholesterol below guideline-recommended goals is defined as an LDL cholesterol level of less than 2.5 mmol/L in primary prevention or less than 1.8 mmol/L in case of secondary prevention.

The inadequacy of treatment options for HoFH was recognised by the US National Lipid Association in 2011 and the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia in 2014, which stated that new agents to lower LDL-C were required for effective treatment of HoFH (2, 115).

Evinacumab is an innovative, novel, first-in-class treatment for people with HoFH. Unlike other treatments such as statins and PCSK9 inhibitors, it is equally effective in people regardless of the genetic nature of their disorder, including people with little or no LDLR activity. Evinacumab delivers a significant and clinically important additional reduction in LDL-C regardless of the background treatments the person is receiving. Moreover, the use of evinacumab may allow for cessation or reduction of less well tolerated drugs, such as lomitapide, or allow for the reduction or discontinuation of LDL apheresis, which is associated with high healthcare resource use and opportunity costs, and significant inconvenience to the patient and/or their carers. For some people with HoFH, evinacumab may be their only possibility at achieving meaningful LDL-C reductions.

B.1.4 Equality considerations

As HoFH is an autosomal dominant inherited condition, there are no implications for inequality based on sex and age. Geographic differences have been reported in the prevalence of HoFH, with higher frequencies found in specific populations, such as French Canadians, Afrikaners in South Africa, and Christian Lebanese receiving stable lipid-lowering therapies, due to “founder effects” [the phenomenon in which a population subgroup has a relative lack of genetic diversity compared to the general population, owing to their descendance from a small number of founding individuals (116)]. In these populations, inherited diseases such as HoFH may be more prevalent than among the general population.

The availability of specialised care, and access to LDL apheresis may be subject to geographical constraints within England and Wales. People from poorer socioeconomic backgrounds find access to care more difficult due to age-related, financial, and employment reasons (117).

The principal comparator of evinacumab (placed at the same line of therapy) is lomitapide. Lomitapide is not indicated for the treatment of adolescents, being suitable only for people ≥18 years and over (6), compared with evinacumab, which is indicated for people ≥12 years. This leaves a significant unmet treatment need in this adolescent population which needs to be addressed. Age is a protected characteristic (7).

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Summary

An SLR was conducted to identify relevant studies to inform the decision problem. The clinical evidence identified for evinacumab in the treatment of people with HoFH consisted of two published studies. These were:

- The ELIPSE trial (study R1500-CL-1629, NCT03399786), a phase 3, randomised, double-blind, placebo-controlled, parallel-group study with a 24-week double-blind treatment period (DBTP) (5) and a 24-week open-label treatment period (OLTP) (118).
- Study R1500-CL-1331 (NCT02265952) (119), a phase 2, open-label, single-arm, proof-of-concept study with the aim of evaluating the safety and efficacy of single and multiple doses of evinacumab in patients with HoFH.

An additional open-label ongoing study (R1500-CL-1719, NCT03409744) reported long-term safety and efficacy data on evinacumab, including patients from R1500-CL-1629 and R1500-CL-1331.

B.2.1.1 Search strategy

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence from the published literature reporting the clinical efficacy, safety, and tolerability of relevant comparator therapies to evinacumab for the treatment of HoFH.

The searches were designed to meet the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (120). Searches were performed on 28 March 2022 with no lower limit on date (i.e., databases were searched since their inception). This search was updated on 13 March 2023, with an additional search undertaken to identify observational and real-world evidence.

Full details of the searches used, and results are provided in Appendix D.

B.2.1.2 Study selection

In the SLR, study selection was consistent with the decision problem (Table 1) for all domains except intervention, which was broadened to include all relevant technologies for the treatment of HoFH. However, for the purposes of this submission, only those technologies reporting on the use of evinacumab, those selected for the indirect treatment comparison (ITC) (Section B.2.9 Indirect and mixed treatment comparisons), and for inputs for the economic analysis were used (Section B.3 Cost effectiveness).

B.2.2 List of relevant clinical effectiveness evidence

In total, three studies were included which informed the decision problem. These were a single-armed proof-of-concept study (R1500-CL-1331, NCT02265952) (11), the parallel placebo-controlled pivotal RCT, ELIPSE (R1500-CL-1629, NCT03399786) (5), and a long-term open-label evaluation study (R1500-CL-1719, NCT03409744) (121). The ELIPSE trial was the principal study that reported comparative data with placebo up to 24 weeks and single-armed data from an open label extension up to 48 weeks (data on file (118)). The characteristics of these studies are summarised in Table 6.

Table 6. Clinical effectiveness evidence.

Study	Study R1500-CL-1331 (Proof-of-Concept)	Study R1500-CL-1629 (Pivotal)	Study R1500-CL-1719 (long-term)
Identifier and reference	Gaudet *et al.* (2017) (11) ClinicalTrials.gov (NCT02265952) (119)	Evaluate the Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia (ELIPSE) DBTP: Raal *et al.* (2020) (5) ClinicalTrials.gov (NCT03399786) (122) OLTP: Data on file (118)	An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Evinacumab in Patients With Homozygous Familial Hypercholesterolemia Gaudet *et al.* (2021) (123) [Conference abstract] ClinicalTrials.gov (NCT03409744) (124) Data on file (121)
Study design	Phase 2, Open-Label, Single-Arm, Proof-of-Concept study	Phase 3, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study	Long-term open label evaluation study
Population	Adults (aged ≥18 years) with HoFH diagnosed by genotyping and phenotyping Participants were excluded if they were unstable on LLT or had commenced LDL apheresis within 4 weeks of screening (n=9 enrolled)	People (aged ≥12 years) with HoFH diagnosed by genotyping and phenotyping Participants were excluded if background LLT (including lipoprotein apheresis) was not stable, or if their LDL-C level was <70 mg/dl, before screening visit. (n=65 randomised)	People (aged ≥12 years) with HoFH diagnosed by genotyping and phenotyping Patients were enrolled from R1500-CL-1331, R1500-CL-1629, or were new (evinacumab naïve) patients
Intervention(s)	Starting dose: evinacumab 250 mg SC. Week 2 to 12: evinacumab 15 mg/kg IV QW Week 13 to 16 (EOT): evinacumab 450 mg SC (n=9)	Evinacumab 15 mg/kg IV Q4W for 24 weeks (DBTP) (n=43) Evinacumab 15 mg/kg IVQ4W for 24 or 48 weeks (OLTP) (n=64)	Evinacumab 15 mg/kg IV Q4W for 24 weeks (ongoing)
Comparator(s)	None (single armed). Longitudinal data reported	Placebo 15 mg/kg IV Q4W for 24 weeks (n=22)	None (single armed). Longitudinal data reported
Indicate if study supports application	Yes	Yes	No

Study	Study R1500-CL-1331 (Proof-of-Concept)	Study R1500-CL-1629 (Pivotal)	Study R1500-CL-1719 (long-term)
for marketing authorisation			
Indicate if study used in the economic model	No	Yes	No
Rationale if study not used in model	Small (n=9) single-armed trial. Phase 3 comparative data available	N/A	Reports data from patients already included in R1500-CL-1331 and R1500-CL-1695 studies. Internal validity of study not as robust as ELIPSE RCT. No equivalent long-term data for comparator
Reported outcomes specified in the decision problem	**Primary** Percent change in LDL-C from baseline (Week 0) to Week 4 **Secondary** Absolute change in LDL-C from Week 2 to Week 4 Percentage and absolute change from baseline in LDL-C over time Absolute change in LDL-C from baseline to Week 4 Percentage and absolute change from baseline in apolipoprotein B, non-HDL-C,TC, and Lp(a) over time Safety endpoints were AEs, including TEAEs and SAEs	**Primary** Percent change in LDL-C from baseline to Week 24 **Secondary** Absolute change in LDL-C from baseline to Week 24 Percent change in apolipoprotein B, non-HDL-C, and TC from baseline to Week 24 Percentage of participants with ≥30% reduction in (LDL-C) at Week 24 Percentage of participants with ≥50% reduction in (LDL-C) at Week 24 Absolute change in apolipoprotein B, non-HDL-C, and TC from baseline to Week 24 Safety endpoints were AEs, including TEAEs and SAEs	**Primary** None specified (not applicable, no hypothesis made) **Secondary** The secondary efficacy analyses evaluated changes in lipid parameters observed with evinacumab treatment, including from patients receiving evinacumab for the first time in this study (New Evinacumab) and those previously exposed to evinacumab (Continue Evinacumab). These are consistent with the ELIPSE trial primary and secondary outcomes
All other reported outcomes	None	Percentage of participants who met United States apheresis eligibility criteria at Week 24 Percentage of participants with LDL-C <100 mg/dL (2.59 mmol/L)	None

Study	Study R1500-CL-1331 (Proof-of-Concept)	Study R1500-CL-1629 (Pivotal)	Study R1500-CL-1719 (long-term)
		Percentage of participants who met European Union apheresis eligibility criteria at Week 24 Percentage of participants with LDL-C <70 mg/dL (1.81 mmol/L) Percent change in apolipoprotein CIII (Apo CIII) from baseline to Week 24	

Abbreviations: AE, adverse event; EOT, end of treatment; DBTP, double blind treatment period; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolaemia; IV, intravenous; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; Lp(a), lipoprotein(a); QW, once a week; OLTP, Open-label treatment period ; Q4W, once every 4 weeks; SAE, serious adverse event; SC, subcutaneous; TC, total cholesterol; TEAE, treatment emergent adverse event.

Two further published studies on evinacumab were identified but not included in the submission. The study by Reeskamp *et al.* (2021) was excluded due to a small sample size (n=4) and as its primary purpose was to investigate the kinetics of the drug rather than its clinical efficacy (125). The study by Stefanutti *et al.* (2022), identified in a hand search, reported on real-world evidence of evinacumab used in an Italian tertiary care setting (126). It reported that evinacumab was associated with substantial and lasting change in LDL-C (-46.8% at 24 months, $p<0.0001$ compared with baseline). However, this study had a small sample size (n=7) and had methodological limitations, for instance in terms of patient selection. Study R1500-CL-1719 was therefore considered to be a more appropriate source of long-term data.

The ELIPSE trial was the sole study on evinacumab that was used to inform the economic model. This study was used in the indirect treatment comparison (ITC) as it was considered to be of high methodological quality (Section B.2.5 Critical appraisal of the relevant clinical effectiveness evidence) and provided comparative data, with a relatively large sample size (n=65). Study R1500-CL-1331 was single armed with few participants (n=9) and was used to establish the licensed dosing regimen. Considering this, study R1500-CL-1331 is included in this section to support the efficacy and safety of evinacumab (Section B.2.3.3 Study R1500-CL-1331 (Proof-of-Concept)), but does not inform the cost-effectiveness analysis for the drug because of its small sample size and lack of comparator. Study R1500-CL-1719 is an ongoing long-term study providing data on the safety and efficacy of evinacumab (121). It has not been used to provide data for the cost-effectiveness of evinacumab because the study was not controlled and lacked the internal validity that was present in the ELIPSE RCT. Additionally, no equivalent long-term data of sufficient robustness exists for the comparator (lomitapide).

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

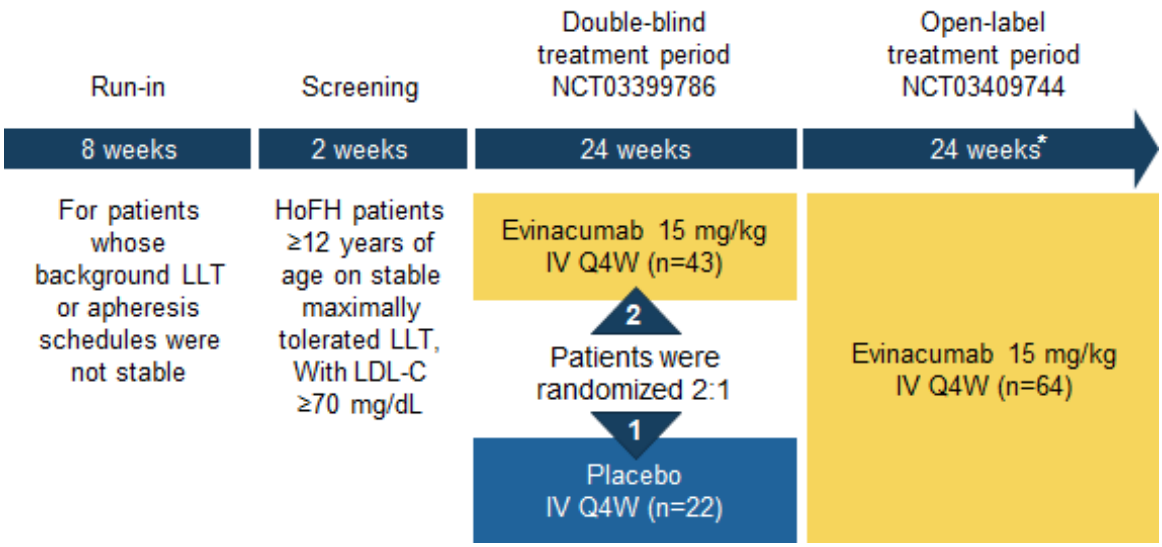
B.2.3.1 ELIPSE trial

The ELIPSE trial has been published by Raal *et al.* (2020) (5). Additional data is reported in the supplementary material of this study, or is provided as academic in confidence (AiC) from the Clinical Study Reports (CSRs) of the trial (118, 127).

B.2.3.1.1 Design

The ELIPSE trial (study R1500-CL-1629) was a phase 3, randomised, double-blind, placebo-controlled, parallel-group study with an 8-week run-in period for patients who did not have a functional diagnosis of HoFH and opted to undergo genotyping for confirmation, or whose background medical lipid lowering therapy (LLT), or apheresis schedules were not stable prior to the 2-week screening period. This was followed by a 24-week double-blind treatment period (DBTP) (5, 127) and a 24-week open-label treatment period (OLTP) (118). The trial protocol is summarised in Figure 11**Error! Reference source not found.**.

Figure 11. Study design of ELIPSE trial (Study R1500-CL-1629).



Abbreviations: IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Q4W, once every 4 weeks. IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Q4W, once every 4 weeks.

*The open-label treatment study was ongoing at the time of database lock for the double-blind treatment period. Data up to 48 weeks is provided in academic confidence.

B.2.3.1.2 Aims

The aim of the ELIPSE trial was to evaluate the efficacy and safety of evinacumab in adult and adolescent patients with HoFH. The primary objective of the study was to demonstrate the reduction of LDL-C by evinacumab 15 mg/kg intravenous (IV) in comparison to placebo

after 24 weeks. Secondary objectives included evaluation of the effect of evinacumab 15 mg/kg IV on other lipid parameters (i.e., ApoB, non-HDL-C, and TC) as well as LDL-C goal attainment and eligibility criteria for LDL apheresis. All objectives and associated endpoints are reported in Table 7.

B.2.3.1.3 Patient enrolment and eligibility

Patients were enrolled from a total of 30 centres spanning 11 countries in Europe, Asia, North America, and Australia (Table 7). The study population primarily consisted of adults ≥18 years of age with HoFH but included 2 adolescent patients with HoFH (≥12 years). Diagnosis of HoFH was based on either genotyping or clinical criteria. The genetic definition included all individuals considered to be true homozygotes. This was defined by the presence of the same mutation(s) in both LDLR, ApoB, PCSK9, or LDLRAP1 alleles; or individuals considered to be compound heterozygotes, defined by the presence of different mutations in the 2 alleles; or double heterozygotes, defined by the presence of mutations in different genes. The study included any patients with HoFH, regardless of their LDLR status, including patients with null/null mutations, defined as having minimal LDLR activity (<15%), and with negative/negative mutations, defined as having mutations such as premature stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations that are predicted to result in the LOF of both LDLR alleles.

Study treatment was added on to the patients' stable background LLT. Patients were on a maximally tolerated statin, ezetimibe, and a PCSK9 inhibitor antibody (unless the patient had a documented reason not to be). Patients receiving LDL apheresis were also included (only weekly or bi-weekly schedules were allowed). Patients were required to maintain stable LLT and a stable apheresis schedule (as applicable). Full eligibility criteria are listed in Table 7.

B.2.3.1.4 Measures taken to minimise bias

Patients were randomised in a 2:1 ratio to receive either evinacumab 15 mg/kg intravenously (IV) or matching placebo, stratified by apheresis treatment (yes or no) and geographical region (Japan and rest of the World). Patients and treating physicians were unaware of the treatment allocation. Both evinacumab and placebo were supplied in physically identical vials with the same withdrawal volume.

Lipid results from blood samples collected after the randomisation visit were not communicated to the sites, and the sponsor's operational team did not have access to these laboratory results until after completion of the DBTP and the first-step analysis. Clinical outcomes, including CV events and suspected treatment emergent adverse events (TEAEs), were adjudicated by a clinical events committee.

B.2.3.1.5 Outcomes

The primary outcome was the percent change in LDL-C from baseline to Week 24. Key secondary outcomes included the absolute change in LDL-C, and the percent change in ApoB, non-HDL-C, and TC from baseline to Week 24. Other secondary endpoints included the percent change in TGs and Lp(a) from baseline to Week 24.

Safety outcomes included AEs, including SAEs, TEAEs, and cardiovascular events pre-defined for adjudication. A full list of specified outcomes is reported in Table 7.

B.2.3.1.6 Open-label extension period (OLTP)

Following completion of the DBTP (at 24 weeks), patients and clinicians were unblinded, and those receiving placebo were given the informed option of receiving evinacumab (15 mg/kg) as part of the OLTP. Final observations were conducted at 48 weeks (118).

B.2.3.1.7 Patient flow

A total of 75 patients were screened and 65 patients were randomized 2:1 to evinacumab 15 mg/kg IV Q4W or placebo (**Error! Reference source not found.**). Of these 65 patients, 64 patients (98.5%) completed the DBTP. One patient in the placebo group withdrew consent and discontinued study treatment early, otherwise all patients completed the double-blind treatment period (5). In total, 64 patients elected to continue treatment with evinacumab in the OLTP (20 of whom had previously received placebo). The patient flow of the ELIPSE trial is reported in Appendix D3.1.

Table 7. Detailed summary of methodology of ELIPSE trial.

Trial number	Study R1500-CL-1629 (Pivotal RCT), ELIPSE RCT
Trial design	Phase 3, multi-centre, randomized, double-blind, placebo-controlled, parallel-group study
Eligibility criteria for participants	**Key genetic inclusion criteria** 1) Documented functional mutation or mutations in both LDLR alleles (Note: patients who had null receptor mutations on both LDLR alleles, i.e., double null,) were eligible, OR 2) Documented homozygous or compound heterozygous mutations in ApoB or PCSK9 (Note: patients who are double heterozygous, i.e., mutations on different genes (e.g., LDLR/PCSK9) and patients with homozygous LDLRAP1 mutations were eligible **Key clinical inclusion criteria** 1) Untreated TC >500 mg/dL (12.93 mmol/L) and TGs <300 mg/dL (3.39 mmol/L), AND 2) Both parents with documented TC >250 mg/dL (6.47 mmol/L) (indicative of heterozygous familial hypercholesterolemia) or patient with cutaneous or tendinous xanthoma before the age of 10 years **Key Exclusion criteria (additional criteria may apply)** 1) LDL-C level <70 mg/dL (1.81 mmol/L) at the screening visit 2) Background medical Lipid Modifying Therapy (LMT) (if applicable) that has not been stable before the screening visit 3) Lipid-apheresis schedule /apheresis settings (if applicable) that have not been stable for at least 8 weeks before the screening visit 4) Use of nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/amount that has not been stable for at least 4 weeks prior to the screening visit 5) Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins 6) Newly diagnosed (within 3 months prior to randomization visit) diabetes mellitus or poorly controlled (HbA1c >9%) diabetes 7) History of a MI, unstable angina leading to hospitalization, coronary artery bypass graft surgery, percutaneous coronary intervention, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, valve replacement surgery, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit 8) Pregnant or breastfeeding women 9) Sexually active women of childbearing potential, who are unwilling to practice a highly effective birth control method prior to the initial dose, during the study, and for 24 weeks after the last dose of study drug 10) Men who are sexually active with women of childbearing potential and are unwilling to consistently use condoms during the study drug treatment period and for 24 weeks after the last dose of study drug regardless of vasectomy status

Trial number	Study R1500-CL-1629 (Pivotal RCT), ELIPSE RCT
Settings and locations where the data were collected	Location (n, number enrolled per country): • United States (6 locations): Boca Raton, Boston, New York, Cincinnati, Portland, Dallas (n=10) • Australia (2 locations): Camperdown, Perth (n=4) • Austria (1 location): Innsbruck (n=2) • Canada (2 locations): Chicoutimi, Quebec (n=3) • France (2 locations): Paris, Marseille (n=5) • Greece (2 locations): Ioannina, Athens (n=4) • Italy (1 location): Napoli (n=7) • Japan (6 locations): Kurome, Nishinomiya, Kanazawa, Suita, Osaka (n=10) • Netherlands (2 locations): Amsterdam, Rotterdam (n=4) • South Africa (1 location): Johannesburg (n=8) • Ukraine (5 locations): Ivano-Frankivs'k, Kharkiv (n=8)
Trial drugs	**Intervention arm** Patients received evinacumab at 15 mg/kg IV Q4W (n=44 following randomisation, 1 additional patient in placebo arm received evinacumab at Week 20 in error). Study drug was provided in 20 mL vials containing evinacumab 150 mg/mL with a minimum withdrawable volume of 15.3 mL. Each vial was labelled as required per country requirement. **Placebo arm (control)** Patients received placebo Q4W (n=22 following randomisation, 1 additional patient in placebo arm received evinacumab at Week 20 in error). Placebo was provided in 20 mL vials with a minimum withdrawable volume of 15.3 mL.
Permitted and disallowed concomitant medication	No specific drugs were not allowed. All patients were required to be stable on background LLT including statins, ezetimibe, PCSK9 inhibitors, and lomitapide. LDL apheresis was also allowed (once or twice weekly).
Primary outcomes (including scoring methods and timings of assessments)	The primary objective of the study was to demonstrate the reduction of LDL-C by evinacumab 15 mg/kg IV in comparison to placebo after 24 weeks in patients with HoFH. The primary endpoint was the percent change in calculated LDL-C from baseline to week 24. The primary endpoint was defined as: 100x (calculated LDL-C value at Week 24 -calculated LDL-C value at baseline)/calculated LDL-C value at baseline (ITT estimand). Primary endpoint analysis was undertaken at baseline, Week 2, Week 4, Week 8, Week 12, Week 16, and Week 24 in DBTP. Primary endpoint analysis was undertaken at Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 in OLTP.

<table>
<tr><th>Trial number</th><th>Study R1500-CL-1629 (Pivotal RCT), ELIPSE RCT</th></tr>
<tr><td>Other outcomes used in the economic model/specified in the scope</td><td>
<table>
<tr><th>Secondary objectives</th><th>Endpoints measured</th></tr>
<tr><td>• To evaluate the effect of evinacumab 15 mg/kg IV on other lipid parameters (i.e., Apo B, non-HDL-C, and TC in patients with HoFH</td><td>• Percent change in Apo B from baseline to Week 24 (ITT estimand)
• Percent change in non-HDL-C from baseline to Week 24 (ITT estimand)
• Percent change in TC from baseline to Week 24 (ITT estimand)
• Percent change in TG from baseline to Week 24 (ITT estimand)
• Percent change in Lp(a) from baseline to Week 24 (ITT estimand)
• Percent change in Apo CIII from baseline to Week 24 (ITT estimand)</td></tr>
<tr><td>• To evaluate the effect of evinacumab on LDL-C goal attainment</td><td>• The proportion of patients with ≥30% and ≥50% reduction in calculated LDL-C at week 24 (ITT estimand)
• The proportion of patients with LDL-C <100 mg/dL (2.59 mmol/L) and <70 mg/dL (1.81 mmol/L) at week 24 (ITT estimand)</td></tr>
<tr><td>• To assess the effect of evinacumab on patients meeting eligibility criteria for apheresis (using German and US apheresis criteria)</td><td>• The proportion of patients who meet EU apheresis eligibility criteria (see German Apheresis Working Group) at Week 24 (ITT estimand)
• The proportion of patients who meet US apheresis eligibility criteria (see US [National Lipid Association] Lipid Apheresis Criteria) at Week 24 (ITT estimand)</td></tr>
<tr><td>• To evaluate the safety and tolerability of evinacumab 15 mg/kg in patients with HoFH</td><td>• Incidence of TEAEs</td></tr>
<tr><td>• To determine concentrations of evinacumab in patients with HoFH</td><td>• Total evinacumab concentrations in serum at selected time points</td></tr>
<tr><td>• To evaluate the potential development of anti-evinacumab antibodies</td><td>• ADA status (positivity, titre and neutralizing activity) over time</td></tr>
<tr><td>• To assess the effect of evinacumab on quality of life using the EQ-5D and HADS QoL questionnaires</td><td>• Response on each EQ-5D item, index score, and change of index score from baseline through Week 24
• Response on HADS from baseline through Week 48</td></tr>
</table>
</td></tr>
<tr><td>Pre-planned subgroups</td><td>Patients were stratified by geographical region and LDL apheresis status during randomisation</td></tr>
</table>

Trial number	Study R1500-CL-1629 (Pivotal RCT), ELIPSE RCT
	Subgroup analysis on the primary outcome was conducted according to demographic characteristics (sex, age, and ethnicity), HoFH genotype, and background treatment

Abbreviations: ADA, anti-drug antibody; Apo B, apolipoprotein B; HADS, Hospital Anxiety and Depression Scale; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; QoL, Quality of Life; TC, total cholesterol; TEAEs, treatment-emergent adverse events.

B.3.2.1.8 Baseline characteristics of participants

The patient population had a mean age of 41.7 years and 53.8% (35 patients) were female. Overall, the demographic and baseline disease characteristics (Table 8), baseline efficacy lipid parameters, and concomitant LLTs (Table 9) were similar between patients randomised to the evinacumab treatment group and the placebo treatment group. Despite 63.1% of patients in the study being treated with at least three lipid-lowering therapies (statin, ezetimibe, PCSK9 inhibitor, lomitapide, LDL apheresis), the patient population had very high baseline LDL-C values (mean 255.1 mg/dL, 6.70 mmol/L) (5). Of the 65 patients randomised, 21 patients were LDLR null/null (LDLR activity <15%) and 12 patients were negative/negative. Consistent with the natural history of HoFH, most patients enrolled into the ELIPSE trial had high levels of CV risk or pre-existing disease. These are reported in Table 10.

Table 8. Demographic characteristics of patients randomised in ELIPSE trial.

	Placebo IV Q4W (n=22)	**Evinacumab 15 mg/kg IV Q4W (n=43)**	**Total (n=65)**
Age, years, mean (SD)	36.7 (11.5)	44.3 (16.8)	41.7 (15.5)
Age category group, years, n (%)			
≥12–<18	1 (4.5)	1 (2.3)	2 (3.1)
≥18–<45	16 (72.7)	23 (53.5)	39 (60.0)
≥45–<65	5 (22.7)	11 (25.6)	16 (24.6)
≥65	0	8 (18.6)	8 (12.3)
Sex, n (%)			
Female	11 (50.0)	24 (55.8)	35 (53.8)
Race, n (%)			
White	17 (77.3)	31 (72.1)	48 (73.8)
Black or African American	0	2 (4.7)	2 (3.1)
Asian	4 (18.2)	6 (14.0)	10 (15.4)
Other, not reported	1 (4.5)	4 (9.3)	5 (7.7)
BMI, kg/m^2, mean (SD)	24.6 (5.7)	26.1 (5.9)	25.6 (5.8)
Any history of CHD, n (%)	21 (95.5)	38 (88.4)	59 (90.8)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; HoFH, homozygous familial hypercholesterolemia; SD, standard deviation.

Table 9. Diagnosis, baseline lipid levels, and background treatment.

	Placebo IV Q4W (n=22)	Evinacumab 15 mg/kg IV Q4W (n=43)	Total (n=65)
Confirmation of HoFH diagnosis (medical history), n (%)			
Genotyping	15 (68.2)	29 (67.4)	44 (67.7)
Clinical diagnosis	7 (31.8)	14 (32.6)	21 (32.3)
LDLR variants null/null <2% activity, n (%)	2 (9.1)	8 (18.6)	10 (15.4)
LDLR variants null/null <15% activity, n (%)	6 (27.2)	15 (34.9)	21 (32.3)
Calculated LDL-C, mg/dL, mean (SD)	246.5 (153.7)	259.5 (172.4)	255.1 (165.2)
ApoB, mg/dL, mean (SD)	175.9 (98.8)	169.1 (82.8)	171.4 (87.8)
HDL-C, mg/dL, mean (SD)	46.0 (16.1)	43.6 (14.9)	44.4 (15.2)
Non-HDL-C, mg/dL, mean (SD)	269.9 (157.8)	281.9 (172.6)	277.8 (166.6)
TC, mg/dL, mean (SD)	315.9 (150.4)	325.6 (170.8)	322.3 (163.1)
TGs, mg/dL, median (IQR)	103.5 (123)	91 (80)	96.6 (97)
Lp(a), nmol/L, median (IQR)	53 (102)	59 (151)	57 (137.0)
LLT, n (%)			
Statin	20 (90.9)	41 (95.3)	61 (93.8)
Ezetimibe	16 (72.7)	33 (76.7)	49 (75.4)
PCSK9 inhibitor	16 (72.7)	34 (79.1)	50 (76.9)
Lomitapide	3 (13.6)	11 (25.6)	14 (21.5)
Lipoprotein apheresis	8 (36.4)	14 (32.6)	22 (33.8)
LLT combinations, n (%)			
Ezetimibe + PCSK9 inhibitor + statin	8 (36.4)	21 (48.8)	29 (44.1)
Ezetimibe + lomitapide + PCSK9 inhibitor + statin	3 (13.6)	4 (9.3)	7 (10.8)
At least three lipid-lowering therapies	11 (50.0)	30 (69.8)	41 (63.1)

Abbreviations: Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; IQR, interquartile range; IV, intravenous; Lp(a), lipoprotein(a); LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, once every 4 weeks; SD, standard deviation; TC, total cholesterol; TG, triglyceride.

Table 10. Pre-existing cardiovascular disease and risk factors.

	Placebo IV Q4W (n=22)	Evinacumab 15mg/kg IV (n=43)	Total (n=65)
Patients with any cardiovascular history/risk factors, n (%)	21 (95.5)	38 (88.4)	59 (90.8)
CHD, n (%)			
Total	12 (54.5)	22 (51.2)	34 (52.3)
Acute myocardial infarction	5 (22.7)	7 (16.3)	12 (18.5)
Silent myocardial infarction	0	0	00
Angina (chronic stable or unstable)	5 (22.7)	15 (34.9)	20 (30.8)
Coronary revascularization procedure	11 (50.0)	16 (37.2)	27 (41.5)
CHD equivalents, n (%)			
Total	1 (4.5)	10 (23.3)	11 (16.9)
PAD	0	4 (9.3)	4 (6.2)
Ischaemic stroke	0	3 (7.0)	3 (4.6)
CKD	0	1 (2.3)	1 (1.5)
Known history of diabetes or 2 or more additional factors	1 (4.5)	2 (4.7)	3 (4.6)
Categorisation of CV risk factors, n (%)			
Very high CV risk*	12 (54.5)	23 (53.5)	35 (53.8)
High CV risk†	10 (45.5)	20 (46.5)	30 (46.2)

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; IV, intravenous; PAD, peripheral arterial disease; Q4W, every 4 weeks.

* Very high CV risk patients were defined as patients with CHD or CHD risk equivalents.

† High CV risk patients were defined as patients without very high CV risk.

B.2.3.2 Study R1500-CL-1719 (interim long-term safety and efficacy)

The R1500-CL-1719 study is an ongoing long-term investigation on the efficacy and safety of evinacumab. Interim results are currently published only as a conference abstract (123). The following section is derived from the interim clinical study report (CSR) and is AiC (121).

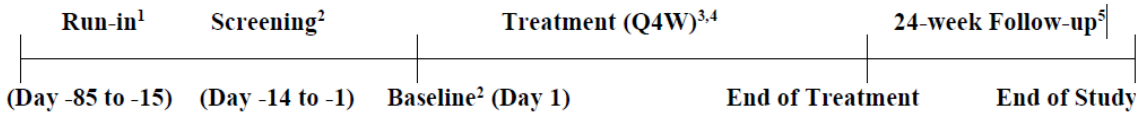
B.2.3.2.1 Design

R-1500-CL01719 is an open-label study designed to evaluate the long-term safety and efficacy of evinacumab in patients with HoFH. Eligible patients for this study were male and female patients ≥12 years of age with HoFH, receiving maximally tolerated LLT. Lipid lowering therapies could include maximally tolerated statin, ezetimibe, PCSK9 inhibitors, lomitapide, and/or lipoprotein apheresis. Patients could include those who had participated in a previous evinacumab study (R1500-CL-1331 and R1500-CL-1629, ELIPSE) and evinacumab-naïve patients with HoFH.

This study consists of a run-in period (for patients who may have required HoFH genotyping, patients whose background medical LLT was not stable prior to screening, or those whose apheresis settings and/or schedule had not been stable). A follow up of up to 192 weeks is planned (124). The study plan is illustrated in

Figure 12.

Figure 12. Study flow diagram.



1. Patients who may require HoFH genotyping and patients whose background lipid lowering therapy/apheresis settings and/or schedule was not stable prior to baseline (day 1) entered an up to 10-week run-in period
2. All patients who were on a stable background lipid lowering therapy entered a 2-week screening period except for those from a previous evinacumab study who completed an end of study visit within 7 days prior to the baseline/day 1 visit for this open-label study
3. Patients who completed an end of study visit in a previous evinacumab study within 7 days of the baseline/day 1 visit for this open-label study did not have to undergo the screening visit and could enroll directly into this study. The end of study visit from the previous study could serve as the baseline/day 1 visit for this open-label study and overlapping assessments did not need to be repeated in this study. Only those assessments and procedures not done in the previous study were to be conducted at the baseline visit
4. Starting on day 1 (baseline), patients received evinacumab 15 mg/kg IV administered Q4W
5. Patients will be followed for 24 weeks after receiving the last dose of study drug

B.2.3.2.2 Aims

The primary objective of the R1500-CL-1719 study was to evaluate the long-term safety and tolerability of evinacumab (administered as 15 mg/kg IV Q4W) in patients with HoFH. An additional objective was to evaluate these outcomes in an adolescent population (aged between 12 and 18 years, discussed in Section B.2.7.4 Use in adolescent patients). Although a specific research hypothesis was not postulated, the primary efficacy outcome of interest was reduction in LDL-C.

B.2.3.2.3 Patient enrolment and eligibility

Participants in R1500-CL-1719 were classified broadly in two ways. Firstly, by age, with participants ≥18 years of age at screening belonging to the adult population, and participants ≥12 but ≤18 years of age at screening belonging to the adolescent population). The total population was the sum of both adult and adolescent groups. Secondly, according to prior exposure to evinacumab:

- New Evinacumab group: patients who had entered the study directly and who had not previously been in an evinacumab study
- Continue Evinacumab group: patients entering this study after completing the R1500-CL-1629 study or R1500-CL-1331 study who had received evinacumab in the parent study
- Total Evinacumab group: the sum of the New Evinacumab and Continue Evinacumab groups

The patient disposition of all enrolled patients (i.e., the total population) are reported in Table 11. In the adolescent group (n=14), 12 patients belonged to the new evinacumab group (i.e., were evinacumab naïve), with 2 patients being recruited from R1500-CL-1629 (ELIPSE).

Table 11. Patient disposition and current status (all patients enrolled).

	New Evinacumab [redacted]	Continue Evinacumab [redacted]	Total Evinacumab [redacted]
Patients Enrolled	[redacted]	[redacted]	[redacted]
Patients enrolled but not treated	[redacted]	[redacted]	[redacted]
Patients enrolled and treated	[redacted]	[redacted]	[redacted]
Completed the treatment period (as per CRF)	[redacted]	[redacted]	[redacted]
Did not complete the treatment period (as per CRF)	[redacted]	[redacted]	[redacted]
Ongoing in treatment period	[redacted]	[redacted]	[redacted]
Completed the study	[redacted]	[redacted]	[redacted]
Did not complete the study	[redacted]	[redacted]	[redacted]
Ongoing in study	[redacted]	[redacted]	[redacted]
Patients participated in the R1500-CL-1331 study	[redacted]	[redacted]	[redacted]
Patients participated in the R1500-CL-1629 study	[redacted]	[redacted]	[redacted]
Patients who were evinacumab-naïve	[redacted]	[redacted]	[redacted]

Abbreviations: CRF, case report form.

B.2.3.2.5 Methods used to minimise bias

The study was open-label and all participants were aware they were receiving evinacumab 15 mg/kg Q4W. The main efficacy outcomes (circulating lipid levels) were objective. A central laboratory was used to minimise bias in measurement.

B.2.3.2.5 Baseline characteristics

The baseline value used for each participant group was defined as the following:

- New Evinacumab: the last obtained value before the first dose of study drug in the study (R1500-CL-1719)
- Continue Evinacumab:
    - For patients who participated in pivotal, Phase 3 evinacumab study R1500-CL-1629 (ELIPSE), baseline was defined as the last obtained value before the first dose of double-blind study drug in that study

- For patients who participated in the proof-of concept, Phase 2 evinacumab study R1500-CL-1331, baseline was defined as the last obtained value before the first dose of study drug in R1500-CL-1719.
  [redacted]

Demographics

The baseline demographics of the included patients are reported in Table 12.

Diagnosis

Patients were entered into this study as evinacumab-naïve patients or from the parent studies (R1500-CL-1331, R1500-CL-1629) based on either clinical criteria or genotyping done prior to study entry.
[redacted].

Genotype status

In terms of genotype status, patients were
[redacted].

Pre-existing cardiovascular disease

The cardiovascular medical history findings in the total population were consistent with underlying HoFH, with the most common findings associated with the patients' CVD. Of the total enrolment of 116 patients,
[redacted].

Background treatment

[redacted]

Table 12. Demographics and baseline characteristics for total population.

	New evinacumab [redacted]	Continue evinacumab [redacted]	Total evinacumab [redacted]
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]
Age category group, years, n (%)			
≥12–<18	[redacted]	[redacted]	[redacted]
≥18–<45	[redacted]	[redacted]	[redacted]
≥45–<65	[redacted]	[redacted]	[redacted]
≥65–<75	[redacted]	[redacted]	[redacted]
≥75		[redacted]	[redacted]
Sex, n (%)			
Female	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other, not reported	[redacted]	[redacted]	[redacted]
BMI, kg/m^2, mean (SD)	[redacted]	[redacted]	[redacted]
LDL-C at baseline			
Calculated LDL-C (mg/dL), mean (SD)	[redacted]	[redacted]	[redacted]
Calculated LDL-C (mmol/L), mean (SD)	[redacted]	[redacted]	[redacted]
CVD history, n (%)			
Patients with any cardiovascular history/risk factors	[redacted]	[redacted]	[redacted]
History of CHD	[redacted]	[redacted]	[redacted]
CHD risk equivalents*	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HoFH, homozygous familial hypercholesterolemia; SD, standard deviation.

* CHD equivalents refers to people with a 10-year risk of coronary death or nonfatal myocardial infarction at least as high as those who have known CHD (including those with stable angina or prior myocardial infarction), which generally exceeds 20%.

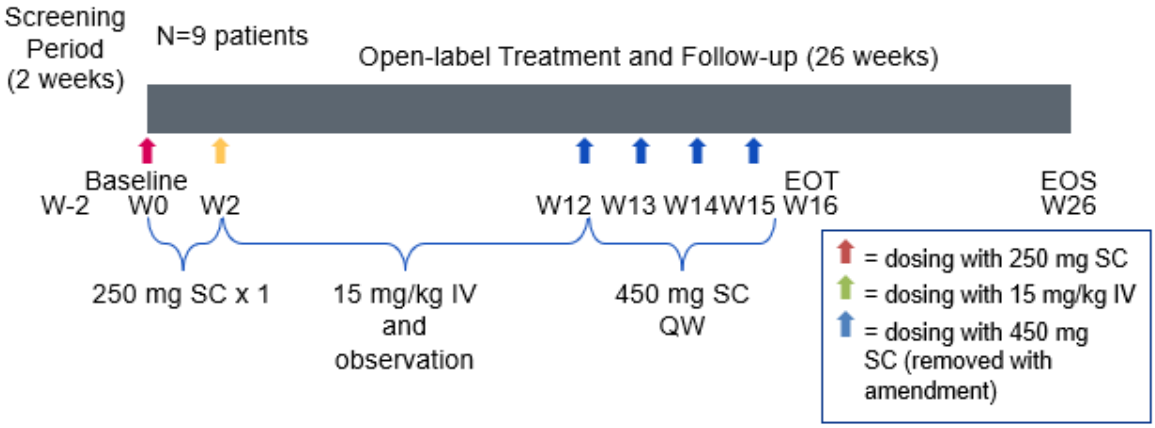
B.2.3.3 Study R1500-CL-1331 (Proof-of-Concept)

Study R1500-CL-1331 (NCT02265952) (119) was a phase 2, open-label, single-arm, proof-of-concept study with the aim of evaluating the safety and efficacy of single and multiple doses of evinacumab in patients with HoFH. This was a small study with 4 periods of implementation; namely run-in, screening (2 weeks), open-label treatment (16 weeks), and observation periods (10 weeks) (Figure 13). Patients (≥18 years) were eligible for enrolment if they had a genetic or clinical diagnosis of HoFH and were stable on treatment.

The primary endpoint was the percent change in LDL-C from baseline (Week 0) to Week 4 (11). Key secondary points were absolute change in LDL-C from Week 2 to Week 4; percentage and absolute change from baseline in LDL-C over time; absolute change in LDL-C from baseline to Week 4; percentage and absolute change from baseline in apolipoprotein B, non-HDL-C, TC, and Lp(a) over time; and AEs, SAEs, and TEAEs. As the R1500-CL-1331 trial was small and exploratory, for the purposes of this submission results from this study are regarded as secondary and supportive only.

The study population consisted of 9 adult patients (5 men and 4 women) with HoFH diagnosed by genotyping and phenotyping. The mean age of the patients was 36 years. Three patients had homozygous null allele mutations, including 2 null homozygotes and one compound heterozygote with two null alleles (11).

Figure 13**. Design of study R1500-CL-1331.**



Abbreviations: EOS, end of study; EOT, end of treatment; IV, intravenous; QW, once every week; SC, subcutaneous; W, week.

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

B.2.4.1 ELIPSE trial

B.2.4.1.1 Estimation of sample size

It was estimated that a sample size of 57 patients (38 assigned to receive evinacumab and 19 assigned to receive placebo) was required to provide a power of 90% to confirm the primary efficacy hypothesis of a between-group absolute difference in the mean percent change in the LDL-C level of 38 percentage points, according to a two-sample t-test with a two-sided significance level of 0.05. This assumption was based on a common standard deviation (SD) of 35% of the percent change from baseline in the two groups, after a 20% adjustment to account for patients who had withdrawn from the trial or could not otherwise be evaluated.

B.2.4.1.2 Datasets analysed

The Efficacy Sets included both the intention-to-treat (ITT) and modified ITT (mITT) populations. The ITT population was defined as all randomised patients who received at least 1 dose or part of a dose of evinacumab in the DBTP, and the mITT population was defined as the randomised population who took at least 1 dose or part of a dose of evinacumab in the DBTP and had an evaluable primary endpoint. Both the ITT and mITT included all 65 randomized patients (100.0%). Three datasets were analysed; these were the efficacy analysis set, safety analysis set (SAF), and a quality of life (QoL) set. The numbers of patients analysed in each set are reported in Table 13.

Table 13. Analysis populations in the ELIPSE trial.

Analysis populations		Placebo IV Q4W (n=22)	Evinacumab 15 mg/kg IV Q4W (n=43)	Total (n=65)
Randomised population		22	43	65
Efficacy analysis dataset	ITT	22	43	65
	mITT	22	43	65
SAF	DBTP	21	44	65
	OLTP	20	44	64
QoL population	EQ-5D	20	43	63
	HADS	20	43	63

Abbreviations: DB, double-blind; HADS, Hospital Anxiety and Depression Scale; ITT, intent-to-treat; IV, intravenously; mITT, modified intent-to-treat; OLTP, open-label treatment period; Q4W, every 4 weeks; QoL, quality of life; SAF, safety analysis set.

B.2.4.1.3 Analysis of primary efficacy outcomes

A mixed-effects model for repeated measures to analyse the percent change from baseline in the calculated LDL cholesterol level at Week 24 in the ITT population. The model included the fixed categorical effects of trial-group assignment (evinacumab vs. placebo), randomisation strata (apheresis [yes vs. no] and geographic region [Japan vs. rest of world]), time point (Week 2, 4, 8, 12, 16, 20, or 24 weeks), and interactions between strata and time point and between treatment and time point, as well as the continuous fixed covariates of the interaction between baseline levels of calculated LDL cholesterol and time point.

B.2.4.1.4 Analysis of secondary efficacy outcomes

The continuous secondary outcomes were analysed using the same model that was used for the primary outcome, except for variables that were anticipated to have a non-normal distribution, including TGs and Lp(a), which were assessed using a robust regression model (128) after applying a multiple-imputation approach (i.e., a log transformation of data before multiple imputation) for handling missing data. In the model, the outcome of interest was the response variable with trial group, randomisation strata, and corresponding baseline values as covariates. Binary outcomes were assessed by logistic regression after the application of a multiple-imputation approach, with the trial group and corresponding baseline values as covariates, stratified according to randomisation strata. The overall type I error was controlled for primary and key secondary outcomes with a hierarchical inferential approach.

B.2.1.4.5 Analysis of safety outcomes

The safety analysis population included all the patients who had undergone randomisation and had received at least one dose of evinacumab or placebo (5). The period for the evaluation of AEs was defined as the interval from the day of administration of the first dose

of evinacumab or placebo until Week 24. All safety data were assessed descriptively. The percent change from baseline in the HDL cholesterol level was assessed descriptively as a safety outcome because of reductions in this measure that had been observed after evinacumab treatment in previous studies.

B.2.4.2 Study R1500-CL-1719 (interim long-term safety and efficacy)

In the R1500-CL-1719 study, four datasets were analysed. The Safety Analysis Set (SAF) included all patients who were enrolled and received at least 1 dose or part of a dose of open-label study treatment in this study. The pharmacokinetic (PK) population included all treated patients who received any study drug and who had at least 1 non-missing evinacumab concentration result following the first dose of study drug. The target (total ANGPTL3) population included all treated patients who received any amount of study drug (SAF) and had at least 1 non-missing total ANGPTL3 measurement following the first dose of study drug. The immunogenicity (anti-evinacumab antibody) population included all treated patients who received any study drug and who had at least 1 non-missing anti-drug antibody (ADA) result following the first dose of study drug.

[redacted]

The R500-CL-1719 study did not seek to address a specific research hypothesis, but was observational in nature, following a cohort of patients receiving evinacumab. Statistics on cohort characteristics were descriptive, with comparisons, where made using standard parametric and non-parametric methods.

B.2.4.3 Study R1500-CL-1331 (Proof-of-Concept)

As a proof-of-concept study, R1500-CL-1331 was exploratory and did not set out to answer a hypothesis. It had a small sample size (n=9). Data from the study was reported descriptively, with limited summary data (mean ± SD) reported on continuous variables such as LDL-C levels.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The quality of the ELIPSE trial (5) was assessed using the RoB2 tool (109) and was found to be at low risk of bias in every domain and at low risk of bias overall (Appendix D).

The long-term safety and efficacy study (R1500-1719) (121) was single-armed, included patients from the ELIPSE trial, is ongoing, and has not been published. Consequently, it has not been formally appraised.

As a proof-of-concept single armed study with a small sample size (n=9), study R1500-CL-1331 was not a good fit for appraisal with any published tool. It was also reported as a research letter which lacked details on the study methodology (11).

B.2.6 Clinical effectiveness results of the relevant studies

Summary

- The principal clinical effectiveness data were derived from the ELIPSE trial, with 43 people randomised to evinacumab (15 mg/kg IV Q4W for 22 weeks) and 22 people randomised to placebo.
    - At 24 weeks in the DBTP, evinacumab was associated with a mean difference of -49.0% (95% CI -65% to -33.1%, *P*<0.001) in circulating LDL-C levels compared with the placebo treatment group. This mean absolute difference between groups in LDL-C levels was -3.4 mmol/L (95% CI -4.5 to -2.3 mmol/L).
    - At 24 weeks in the DBTP, there were also changes in other lipid parameters associated with evinacumab including ApoB (-36.9%), non-HDL-C (-51.7%) TC (-48.4%), and Lp(a) (-1.9%).
    - In the OLTP of the trial, where participants receiving placebo were switched to evinacumab, the percentage change in LDL-C from baseline to Week 48 was [redacted] for the double-blinded evinacumab patients (n=44). For evinacumab naïve patients, who received evinacumab starting at Week 24 (n=20), the percentage change in LDL-C from baseline to Week 48 was [redacted].
- The ELIPSE trial was assessed as being of high methodological quality at low risk of bias using the ROB-2 tool.
- The R1500-CL-1719 study reported longitudinal data that showed lipid parameter reductions associated with evinacumab were [redacted], with a [redacted] at this timepoint. [redacted].
- The results of Study R1500-CL-1331 were consistent with the ELIPSE trial, with the mean percent change in LDL-C from baseline being -49% at Week 4 and -52% at Week 6 (maximal reduction achieved).

The following outcome data, specified in the scope, were reported in the ELIPSE trial (R1500-CL-1629) DBTP (5, 127) and OLTP (118). Interim longer-term efficacy data were reported by R1500-CL-1719 (121). Results data from the R1500-CL-1331 proof-of-concept study (11) are reported separately in Section B.2.6.3 Study R1500-CL-1331 (Proof-of Concept study).

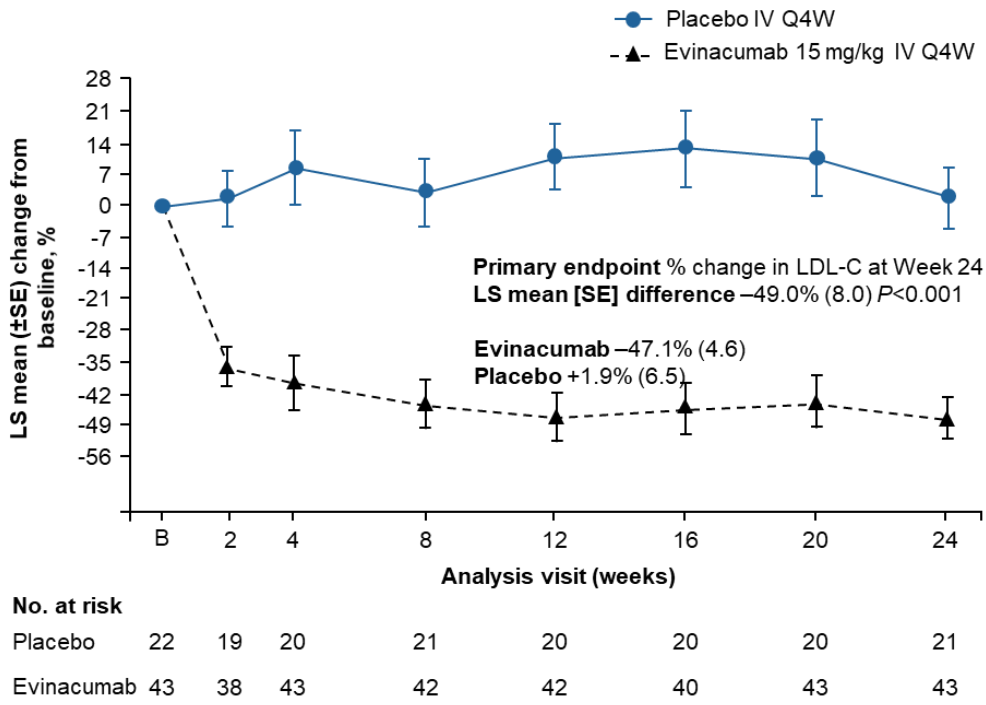
B.2.6.1 Changes in LDL-C levels (primary endpoint)

B.2.6.1.1 Results from ELIPSE (R1500-CL-1629)

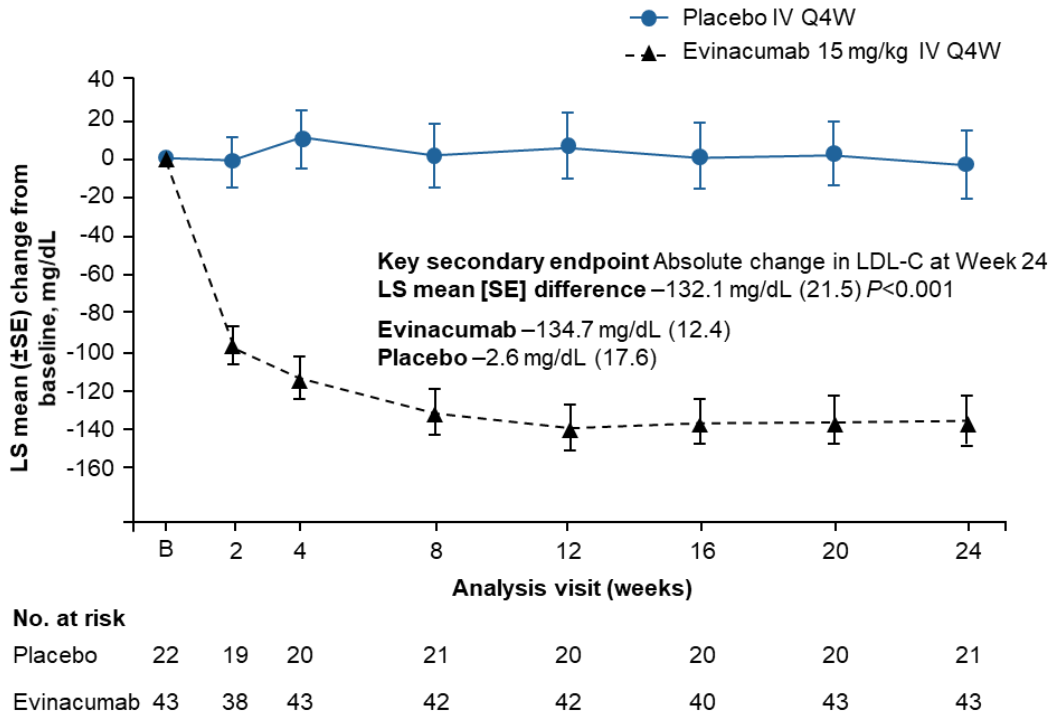
The primary outcome of the ELIPSE trial was the percent change in calculated LDL-C from baseline to Week 24 (5). Evinacumab demonstrated significant and clinically meaningful reductions in LDL-C versus placebo in patients with HoFH. The primary efficacy outcome was met with a least squares (LS) mean difference of -49.0% (95% CI -65 to -33.1%, *P*<0.001) for evinacumab versus placebo treatment groups. The LS mean percent change from baseline in calculated LDL-C at Week 24 was -47.1% in the evinacumab treatment group compared with +1.9% in the placebo group. At Week 24, the LS mean absolute change from baseline in calculated LDL-C was -134.7 mg/dL (-3.48 mmol/L) for the evinacumab treatment group compared with +2.6 mg/dL (+0.07 mmol/L) for the placebo group. Longitudinal data showing changes in relative and absolute LDL-C is reported graphically in Figure 14 (5).

Figure 14. (A) Percent and (B) absolute change in LDL-C (Study R1500-CL-1629).

(A)



(B)



Abbreviations: IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LS, least squares; Q4W, every 4 weeks; SE, standard error.

The longer-term efficacy of evinacumab was investigated in the OLTP of the trial, where participants receiving placebo were switched to evinacumab. During the OLTP, the percentage change in LDL-C from baseline to Week 48 was [redacted] for the double-blinded evinacumab patients (n=44). For double-blinded placebo patients who received evinacumab in the OLTP starting at Week 24 (n=20), the percentage change in LDL-C from baseline to Week 48 was [redacted] (***[redacted].

[redacted].

[redacted]

[redacted]

Abbreviations: IV, intravenous; LDL-C, low-density lipoprotein cholesterol; Q4W, every 4 weeks; SE, standard error.

B.2.6.1.2 Longer-term data from R1500-CL-1719

The R1500-CL-1719 is an ongoing long-term study on the safety and efficacy of evinacumab with a planned follow up of up to 192 weeks (121, 124). Patient enrolment were derived from two previous studies, primarily the ELIPSE trial (R1500-CL-1629) ([redacted]), and also the smaller proof-of-concept trial (R1500-CL-1331) ([redacted]), as well as evinacumab naïve patients ([redacted]). The disposition of patients is detailed in Table 11.

Complete interim data illustrating the longitudinal change in LDL-C from baseline is illustrated in ***[redacted]

[redacted].

[redacted]

[redacted]

The most plausible mechanism for loss of longer-term efficacy in biological drugs is due to the development of neutralising antibodies (NAb) (129). These were measured throughout the R1500-CL-1719 study.

[redacted]

Abbreviations: LDL-C, low-density lipoprotein cholesterol; SE, standard error.

The relative and absolute reduction in LDL-C associated with evinacumab up until 120 weeks is reported in *** This is based on data reported in Table 26 of the CSR (121). This more accurately reflects the immediate efficacy and durability of response associated with evinacumab, [redacted]

In the total population, treatment with evinacumab resulted in a [redacted]

In patients who previously participated in pivotal Phase 3 study R1500-CL-1629 (ELIPSE), longer-term [redacted] when looking at longitudinal results across both studies. Beyond the initial 48 weeks of evinacumab treatment, [redacted].

[redacted]

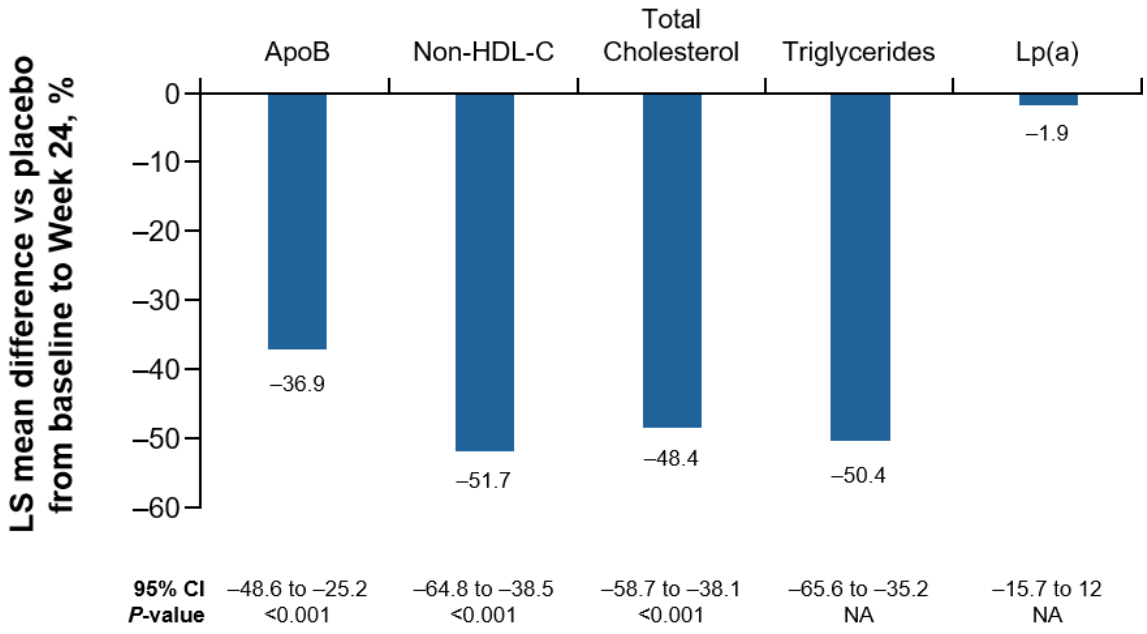
[redacted]

B.2.6.2 Secondary outcomes

B.2.6.2.1 ELIPSE trial

Treatment with evinacumab in patients with HoFH resulted in significant percent changes from baseline in apolipoprotein B, non-HDL-C, TC, and TGs at Week 24 compared with placebo (all P<0.001) (Figure 18). Evinacumab also resulted in an approximately -30% change in HDL-C at Week 24.

Figure 18. LS mean difference versus placebo from baseline to Week 24.



Abbreviations: ApoB, apolipoprotein B; CI, confidence interval; Lp(a), lipoprotein(a); LS, least squares; non-HDL-C, non-high-density lipoprotein cholesterol.

Results of other clinical secondary outcomes (proportions based on dichotomous outcomes) at Week 24 are reported in Table 14. Significantly greater percentages of patients in the evinacumab group compared with the placebo group achieved ≥30% and ≥50% reduction in LDL-C (83.7% vs 18.2% and 55.8% vs 4.5%, respectively) and LDL-C <100 mg/dL (46.5% vs 22.7%). In addition, the percentage of patients who met US lipoprotein apheresis eligibility criteria (LDL-C ≥300 mg/dL) was significantly greater in the placebo group compared with the evinacumab group (5).

Table 14. Additional secondary efficacy analyses from baseline to Week 24.

	Placebo IV Q4W (n=22)	Evinacumab 15 mg/kg IV Q4W (n=43)	Odds ratio	95% CI	*P*-value‡
Patients with ≥30% reduction in LDL-C	18%	84%	25.2	5.7-110.5	<0.001
Patients with ≥50% reduction in LDL-C	5%	56%	24.2	3.0-195.6	0.003
Proportion of patients who met US lipoprotein apheresis eligibility criteria†	23%	7%	0.1	0.0-1.3	0.09
Proportion of patients with LDL-C <100 mg/dL	23%	47%	5.7	1.3-24.9	NA

Abbreviations: CI, confidence interval; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; Q4W, once every 4 weeks.

† A patient is considered as meeting US lipoprotein apheresis eligibility criteria if LDL-C ≥300 mg/dL (7.77 mmol/L).

‡ P-value is based on the odds ratio.

EQ-5D utility scores at both baseline and at Week 24 are presented in Table 15. Reductions in mean utility score were observed in both the placebo and evinacumab arms at Week 24, however these are not statistically significant. Results can be likely explained by the insensitivity of the EQ-5D measure in this patient population, due to the episodic nature of the condition, i.e., QoL being more dependent on CV events rather than direct LDL-C change.

Table 15. Quality-of-life analysis set - EQ-5D utility scores.

	Placebo IV QW4 (n=20)	Evinacumab 15mg/kg IV Q4W (n=43)
Utility score, baseline		
n Mean (SD) Median Q1:Q3 Min:Max	20 0.8577 (0.23081) 0.9240 0.7960 : 1.0000 -0.008 : 1.000	43 0.8977 (0.16161) 1.0000 0.7960 : 1.0000 0.193 : 1.000
Utility score, Week 24		
n Mean (SD) Median Q1:Q3 Min:Max	20 0.7984 (0.23923) 0.8480 0.7250 : 1.0000 0.186 : 1.000	43 0.8788 (0.16254) 1.0000 0.7960 : 1.0000 0.193 : 1.000
Utility score, change from baseline to Week 24		
n Mean (SD) Median Q1:Q3 Min:Max	20 -0.0593 (0.16054) 0.0000 -0.1365 : 0.0000 -0.541 : 0.194	43 -0.0189 (0.10926) 0.0000 0.0000 : 0.0000 -0.309 : 0.275

B.2.6.2.2. Study R1500-CL-1719 (interim long-term study)

Results from the R1500-CL-1719 study reported [redacted].

[redacted]

B.2.6.3 Study R1500-CL-1331 (Proof-of Concept study)

The results of the R1500-CL-1331 study were consistent with the ELIPSE study. Patients with HoFH experienced clinically meaningful reductions in the primary efficacy endpoint (percent change in LDL-C) with evinacumab treatment. The mean percent change in LDL-C from baseline was -49% at Week 4 and -52% at Week 6, which was the maximum percent reduction observed with evinacumab (11). Key parameters are reported in Table 16.

Table 16. Baseline lipid-related parameters and change in efficacy endpoints from baseline to Week 4.

Characteristic, mean ± SD or median (Q1, Q3)	Baseline lipid-related parameters		Week 4 efficacy parameters	
	All patients (n=9)	Homozygous null allele mutation (n=3)	Percent change, mean ± SD (n=9)	Absolute change, mean ± SD (n=9)
LDL-C (mg/dL)	376 ± 241	599.4 ± 247.5*	-49 ± 23	-157 ± 90
TGs (mg/dL)	80 ± 41	106.3 (44.3, 106.3)*	-47 ± 17	-181 ± 87
HDL-C (mg/dL)	39 ± 14	30.9 ± 11.6*	-36 ± 16	-15 ± 11
TC (mg/dL)	431 ± 236	–	-47 ± 19	-181 ± 87
Non-HDL-C (mg/dL)	392 ± 246	–	-49 ± 22	-166 ± 93
Lp(a) (nmol/L)	155 ± 109	–	-11 ± 24	-21 ± 93
ApoA1 (mg/dL)	110 ± 24	–	-39 ± 9	-43 ± 17

ApoB (mg/L)	226 ± 132	–	–46 ± 18	–96 ± 56
PCSK9 (ng/mL)	3160 ± 3481		–26 ± 11	–658 ± 845

Abbreviations: Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; Q, quartile; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation; TC, total cholesterol; TG, triglyceride.

*Values are from data on file and originally reported in mmol/L.

B.2.7 Subgroup analysis

Summary

- In the ELIPSE DBTP, treatment with evinacumab resulted in an approximately -50% mean change in LDL-C from baseline to Week 24 for patients with HoFH, regardless of their genotype (null/null and not null/null).
- Treatment with evinacumab was effective at reducing LDL-C levels regardless of the background therapy used, including use of statins, ezetimibe, PCSK9 inhibitors, lomitapide, and LDL apheresis.
- A subgroup analysis of the R1500-CL-1719 study in adolescents (patients aged between 12 and 18 years) reported that the short and long-term efficacy of evinacumab was at least as effective in this group as it was in adults or the total population dataset.

In the ELIPSE study, *a priori* subgroup analyses were conducted on patient characteristics and baseline lipid levels; by patient genotype (consistent with the scope); and by background LLT. The efficacy of evinacumab in adolescent populations (age between 12 and 18 years) was explored in the R1500-CL-1719 trial. Subgroup analyses of individuals according to CV risk were not undertaken (in accordance with the decision to use LLT being based on underlying LDL-C levels, not underlying CV risk or history of CVD).

B.2.7.1 Patient characteristics at baseline

The general relationship observed in the primary analysis of greater reductions in LS mean calculated LDL-C from baseline to Week 24 in the evinacumab treatment group compared with the placebo treatment group was observed for all categories in the following subgroups: gender (male or female); ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported); randomisation region (Japan or rest of the World [ROW]); apheresis status; and baseline calculated LDL-C (<130 mg/dL [3.36 mmol/L] or ≥130 mg/dL [3.36 mmol/L]). Full results are presented in Appendix E.

B.2.7.2 Primary efficacy outcome by genotype

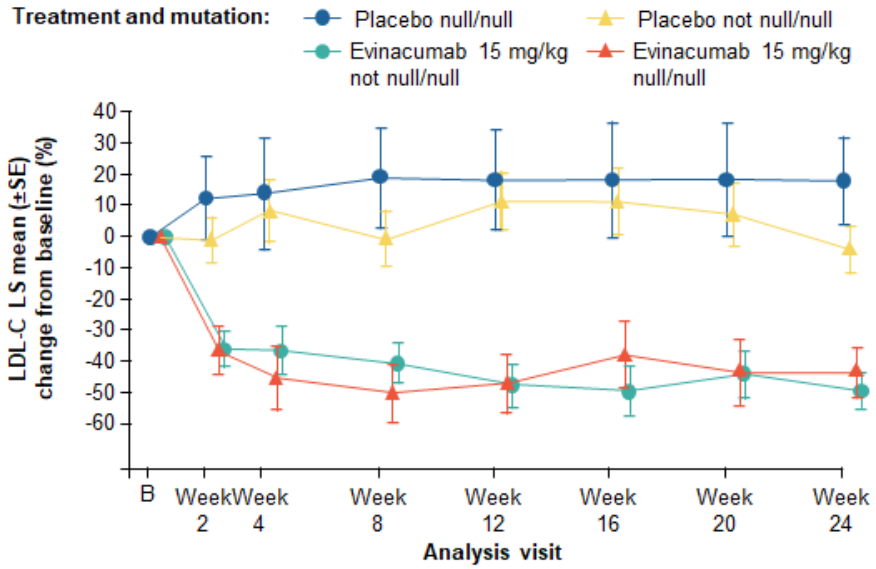
All randomized patients with HoFH were included in this study, regardless of their LDLR genetic mutations. There were 21 patients (32.3%) enrolled in the ELIPSE study with mutations phenotypically characterized as null/null with minimal LDLR activity (defined as <15% based on in vitro assessments of functionality as reported in the literature (12). There were 12 patients (18.5%) enrolled with negative/negative mutations, defined as stop codons, frame shifts, splice site changes, small and large insertions/deletions and copy number variations resulting in the LOF of both LDLR alleles. The mean baseline LDL-C for patients with null/null mutations was 311.5 mg/dL (8.06 mmol/L), and for patients with negative/negative mutations it was 289.4 mg/dL (7.48 mmol/L). This was considerably higher than the mean LDL-C for those patients not considered to have these mutations (246.5

mg/dL [6.39 mmol/L] for the whole cohort). The high mean baseline LDL-C observed in these HoFH subpopulations highlights the severity of disease in this group of difficult-to-treat patients, and is consistent with prior studies showing that these patients have relatively higher LDL-C levels than patients with non-null/null and non-negative/negative mutations, as well as being less responsive to many LLTs (130).

Treatment with evinacumab resulted in an approximately -50% mean change in LDL-C from baseline to Week 24 for patients with HoFH, regardless of their genotype (Figure 19). This percent change translates to an absolute mean change in LDL-C of approximately -158.8 mg/dL (-4.11 mmol/L) for patients with null/null mutations and -142.0 mg/dL (-3.67 mmol/L) for patients with negative/negative mutations (5, 131).
[redacted]). These data are reported on an individual patient level as waterfall plots in

Figure 20.

Figure 19. Calculated LS mean (±SE) percent change in LDL-C from baseline to Week 24 by null/null mutation status in both LDLR alleles.



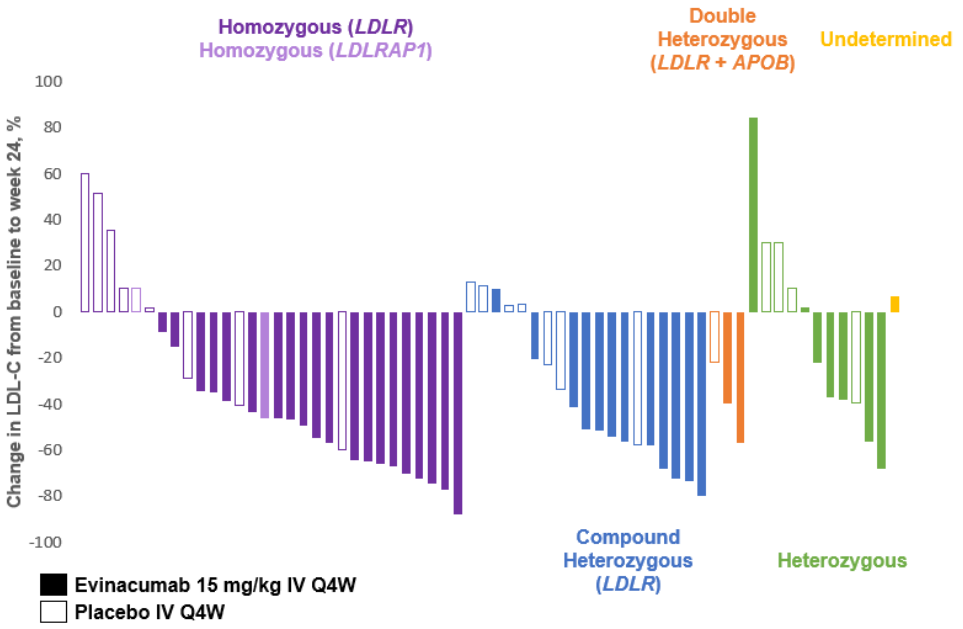
No patients								
P null/null n=6	5	4	5	5	5	5	5	5
P not null/null n=16	16	15	14	15	14	14	14	15
E 15 mg/kg null/null n=15	15	14	15	15	14	15	15	15
E 15 mg/kg not null/null n=28	28	24	28	27	28	25	28	28

Legend: Data are for the <15% LDLR activity population. LS means and SEs are taken from a mixed-effect model with repeated measures approach with the fixed categorical effects of treatment group, randomization strata (lipoprotein apheresis [yes/no] and region [Japan, rest of world]), subgroup factor, time point, treatment-by-time point interaction, strata-by-time point interaction, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction. Data adapted from Raal *et al.* (2020) (5).

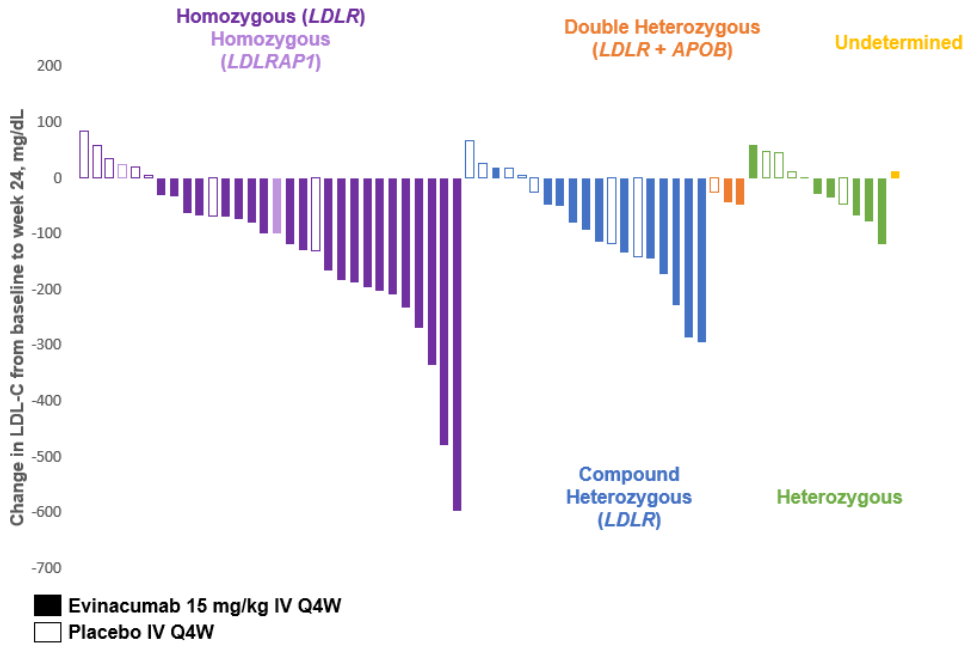
Abbreviations: B, baseline; E, evinacumab; LDL, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LS, least squares; P, placebo; SE, standard error.

Figure 20. Waterfall plots for individual patient (A) percent and (B) absolute changes in LDL cholesterol.

(A)



(B)



Legend: Data from Raal *et al.* (2020) (5).

Abbreviations: ApoB, apolipoprotein B; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LDLRAP1, low-density lipoprotein receptor adaptor protein 1; Q4W, every 4 weeks.

B.2.7.3 Primary efficacy outcome by background LLT

Regardless of background LDL-C-lowering therapies (statins, ezetimibe, PCSK9 inhibitor, lomitapide, lipoprotein apheresis), evinacumab resulted in an approximate -50% mean change in LDL-C from baseline to Week 24, indicating a significant and clinically meaningful reduction in LDL-C for all patients with HoFH (Table 17).

Table 17. Percent change in LDL-C from baseline to Week 24 by background LLT.

Background therapy at baseline, mean (SD)*	Background therapy at baseline		No background therapy at baseline	
	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W
Statin	n=61		n=4	
	2.2 (32.3)	-47.3 (30.6)	-5.7 (22.7)	-46.2 (11.0)
Ezetimibe	n=49		n=16	
	-2.0 (30.6)	-53.1 (21.0)	12.2 (34.1)	-28.0 (45.5)
Lomitapide	n=14		n=51	
	-17.2 (47.6)	-49.6 (22.5)	4.5 (28.4)	-46.4 (32.3)
PCSK9 inhibitor	n=50		n=15	
	1.7 (30.3)	-49.5 (31.9)	0.7 (36.2)	-38.9 (20.1)
Lipoprotein apheresis	n=22		n=43	
	-7.3 (34.3)	-46.2 (18.1)	6.8 (29.2)	-47.8 (34.4)

Abbreviations: IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, once every 4 weeks; SD, standard deviation.

* Patients taking these medications with or without other medications.

Data from Raal et a. (2020) (5).

B.2.7.4 Use in adolescent patients

Two patients from the ELIPSE trial were aged between 12 and 18 years (127), which was an insufficient sample size to perform meaningful analysis. The percent change from baseline in LDL-C at Week 24 for the single adolescent patient treated with evinacumab was -73.3% and was +60% for the single adolescent patient treated with placebo. Both adolescent patients were null/null (data on file). The long-term safety and efficacy study (R1500-CL-1719) enrolled [redacted] The most current results are reported in ***[redacted]

[redacted]

Abbreviations: LDL-C, low-density lipoprotein cholesterol; SE, standard error.[redacted]

Thus, from these data it can be concluded that evinacumab [redacted]. [redacted] adolescents might be expected to benefit more than adults by reducing exposure to LDL-C and atherosclerosis at an earlier age, and thus reducing future CV events (according to the "earlier the better" maxim).

B.2.8 Meta-analysis

No meta-analyses have been conducted.

B.2.9 Indirect and mixed treatment comparisons

Summary

- There are no head-to-head studies that have compared the relative efficacy and safety of evinacumab with a comparator treatment. An indirect comparison was therefore undertaken, using the ELIPSE trial (with IPD) as the index study, with lomitapide as the main comparator of interest.
- As data for lomitapide were restricted to a single-arm trial, a MAIC was performed, with propensity matching controlling for age, history of CHD, and baseline LDL-C. Sensitivity analysis included removing patients receiving lomitapide from the ELIPSE IPD.
- In the base case, evinacumab was associated with a change in LDL-C of -55.08% (96% CI -71.90% to -38.27%) compared with a change of 40.1% (95% -51.5% to 28.7%) for lomitapide, using ITT data. This difference was not statistically significant. There were insufficient data to estimate the comparative effect in lomitapide naïve patients from the ELIPSE trial.
- A Bucher ITC comparing evinacumab with evolocumab (TESLA B trial) found evinacumab to be statistically superior in reducing LDL-C, with a mean difference of -24.33% (95% CI -47.50% to -1.15%). A MAIC also reported evinacumab to be superior to ezetimibe.
- The principal limitation of these analyses was small sample sizes resulting in low estimated sample sizes (ESS), meaning the effects of background treatments could not be controlled for, as well as increasing the overall level of uncertainty in the estimates. This confounds interpretation of the results.
- The results should be considered in the wider context of the comparison between the interventions. Namely, there is less uncertainty in the efficacy of evinacumab compared with lomitapide (which has limited evidence base), evinacumab has a more favourable profile compared with lomitapide, evinacumab is more effective compared with evolocumab, (with numerical data and trends also suggesting higher effectiveness compared with lomitapide), evinacumab has a broader indication compared with evolocumab (not effective in null-null patients), and lomitapide (poorly tolerated, not indicated in adolescents).

B.2.9.1 Rationale and aims

The principal evidence for the safety and efficacy of evinacumab is derived from the ELIPSE RCT (5) (Section B.2.3.1 ELIPSE trial. This was a pragmatic trial in that participants continued with optimal background treatment for HoFH following randomisation to evinacumab or placebo. Evinacumab significantly reduced LDL-C levels by approximately 50% regardless of the underlying mutation or background therapy type (Section B.2.7 Subgroup analysis).

In clinical practice it is anticipated that evinacumab would be used to treat HoFH and potentially allow for the cessation of other treatments, specifically lomitapide, which has an unfavourable adverse safety profile (

Figure 9). However, the ELIPSE trial did not report head-to-head data with any comparator, and, because of this, an indirect treatment comparison (ITC) was undertaken. The overall objective of these analyses was to estimate the relative effects of evinacumab compared with relevant comparator treatments for patients with HoFH to estimate the relative efficacy, safety, and tolerability of evinacumab compared with:

- Lomitapide (Lojuxta®)
- Ezetimibe
- Evolocumab (Repatha®)
- LDL apheresis

The primary comparator of interest was with lomitapide, as this was the comparator used in the *de novo* cost-effectiveness model (CEM) reflecting the positioning of evinacumab in the pathway of care (Section **Error! Reference source not found.** The primary endpoint of interest was the percent reduction in LDL-C. Data from the ITC also informed the efficacy of the background treatments ezetimibe, evolocumab, and LDL apheresis used to inform the CEM (Section B.3.3 Clinical parameters and variables). By measuring the relative effect of each technology, their effect on LDL-C could be modelled separately, allowing for different combinations of drugs to be used in the model.

B.2.9.2 Studies identified on comparators

The ELIPSE trial was used as the index trial (5). Studies on potential comparators were identified from the SLR (Section B.2.1 Identification and selection of relevant studies, Appendix D). A review of study heterogeneity was undertaken following which studies were assessed for suitability for ITC. Studies were excluded mainly based on the population or sample size (<10 patients) or study design, with, for instance, retrospective observational studies being deemed unsuitable. Where more than one study was identified that was applicable, the study adjudicated to be of higher methodological quality and lower risk of bias was preferred. Full information on study selection is reported in Appendix D section 2.2.

Four studies were selected for the ITC, reporting on treatment of people with HoFH using lomitapide (87), evolocumab (78), and ezetimibe (75), with the former study being an open-label single-armed trial, and the latter two studies being RCTs. No suitable studies were identified on LDL apheresis. As lomitapide was the comparator used in the CEM, and therefore data pertaining to it is equally important as that from the ELIPSE trial, the design and methodological quality of this trial is considered in detail in Section B.2.9.3 . The patient characteristics of the included studies, compared with the ELIPSE RCT, are reported in Table 18. Baseline lipid parameters are reported in Table 19.

Table 18. Characteristics of studies included for ITC.

Study	Treatment	Sample size	Age		Female n (%)	Coronary heart disease n (% yes)	Baseline apheresis n (% yes)	Baseline statins n (% yes)	Baseline ezetimibe n (% yes)	Homozygous LDL-R mutation status		
			Mean (SD)	Median (min, max)						Defective/ defective n (%)	Negative/ negative n (%)	Null/null n (%)
ELIPSE Raal (2020) (5)	Evinacumab	43	44.3 (16.8)	41.0 (15, 75)	24 (55.8)	22 (51.2)	14 (32.6)	41 (95.3)	33 (76.7)	17 (39.5)	4 (9.3)	15 (34.9)
	Placebo	22	36.7 (11.5)	39.5 (12, 55)	11 (50.0)	12 (54.5)	8 (36.4)	20 (90.9)	16 (72.7)	2 (9.1)	5 (22.7)	6 (27.3)
Cuchel (2013) (87)	Lomitapide	29	30.7 (10.6)	NR	13 (44.8)	21 (72.4)[b]	18 (62.1)	27 (93.1)	22 (75.9)	NR	NR	NR
Gagne (2002) (75)	Ezetimibe + statin	33	32 (3)[a]	31 (NR, NR)	17 (51.5)	15 (45.5)[c]	17 (51.5)	NR	NR	NR	NR	NR
Raal (TESLA Part B [2015]) (78)	Evolocumab	33	30 (12)	NR (13, 51)	16 (48.5)	15 (45.5)[b]	NR (NR)	33 (100)	30 (91.0)	8 (24.24)	1 (3.0)	20 (60.6)
	Placebo	16	32 (14)	NR (14, 57)	8 (50.0)	6 (37.5)[b]	NR (NR)	16 (100)	15 (94.0)	5 (31.25)	0 (0.0)	8 (50.0)

Abbreviations: HoFH, homozygous familial hypercholesterolemia; ITC, indirect treatment comparison; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; n, number of patients; NR, not reported; SD, standard deviation.

[a] Standard error used as SD not reported.

[b] Reported as coronary artery disease.

[c] Reported as premature coronary heart disease. Two LDL apheresis studies were excluded from the ITC due to a lack of patient baseline data for adequate population adjustment required in the ITC.

Table 19. Summary of baseline lipid parameters.

Study	Treatment	Sample size	LDL-C (mg/dL) Mean (SD)	Apo-B (mg/dL) Mean (SD)	Non-HDL-C (mg/dL) Mean (SD)
ELIPSE	Evinacumab	43	259.5 (172.4)	169.1 (82.75)	281.9 (172.61)
	Placebo	22	246.5 (153.7)	175.9 (98.76)	269.9 (157.81)
Raal (TESLA Part B [2015])	Evolocumab	33	355.8 (135.2)	210 (70)	375.1 (135.3)
	Placebo	16	336.4 (146.9)	210 (80)	359.6 (150.8)
Cuchel (2013)	Lomitapide	29†	336.4 (112.1)	260 (80)	386.7 (131.5)
Gagne (2002)	Ezetimibe + statin	33	313 (22)*	253 (14)†	NR (NR)

Abbreviations: Apo-B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; ITC, indirect treatment comparison; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor; NR, not reported; SD, standard deviation.

* Intention to treat dataset.

† Standard error used as standard deviation not reported. Two LDL apheresis studies were excluded from the ITC due to the lack of patient baseline data for adequate population adjustment required in the ITC.

B.2.9.3 Pivotal study on lomitapide (Cuchel *et al.* 2013)

The comparison with lomitapide was particularly germane as it was considered that evinacumab could replace lomitapide in the treatment of indicated individuals (

Figure 9). The comparison with lomitapide was made using the pivotal trial reported by Cuchel *et al.* (2013) (87). This is considered in the domains of B.2.9.3.1 Study design, B.2.9.3.3 Patient attrition, B.2.9.3.4 Analysis datasets, B.2.9.3.6 Results, and an overall assessment of study quality (Section B.2.9.3.7 Critical appraisal).

B.2.9.3.1 Study design

The pivotal trial by Cuchel *et al.* (2013) (87), listed in ClinicalTrials.gov as NCT00730236, was a single-armed trial that had a follow-up period of 56 weeks. The trial followed on from the proof-of-concept dose-escalation study (132), which reported that lomitapide was associated with a mean change in LDL-C of -51% in six patients. The pivotal trial was followed up to a maximum of 294 weeks in an extension study reported by Blom *et al.* (2016) (107) (NCT00943306) and additional analyses were reported by Stefanutti *et al.* (2015) (133), Averna *et al.* (2016) (134), and Blom *et al.* (2018) (135).

The authors of Cuchel *et al.* (2013) acknowledged that the main limitation of the study is the fact it was single-armed and open-label, as this "could bias the interpretation of the efficacy data" (87). The justification for this approach was to maximise throughput of patients receiving the drug, particularly for safety monitoring, and because, in their opinion, the proof-of-concept study (132) indicated the effect size was sufficiently large to be inferred from longitudinal data alone. To partly mitigate against the inevitable bias of this design type, the researchers introduced a 6-week run in period with the intention of stabilising background medication, introducing the required low-fat diet, and stabilisation of pre-treatment LDL-C levels. This approach is similar to using an interrupted time series as a quasi-experimental alternative to a parallel control group (136).

However, there continued to be limitations in using this approach. Firstly, some patients dropped out at the run-in stage, but were not accounted for in the final analysis (see Section B.2.9.3.3 Patient attrition). Secondly, as the study was open-label, the possibility of detection bias affecting results was present (137). However, this is less likely to be a significant problem with the measurement of LDL-C, which is a hard objective endpoint. But most importantly, thirdly, it does not allow for the control of confounding factors such as the Hawthorne effect (138), which may be important since participant behaviour (e.g., adherence to the required strict diet) could influence the primary outcome.

Whilst the authors' rationale for this design was understandable, and the use of single-armed studies are increasingly acceptable in health technology assessment (HTA) (139), they are not a substitute for randomised controlled trials (RCTs), which are considered the gold standard in measuring the efficacy of interventions (140). Although there were technical difficulties in undertaking RCTs in this population, other technologies that have been developed in the previous decade have successfully measured the clinical efficacy of drugs using this trial design. This includes the TESLA B study (evolocumab) (78), ODYSSEY study (arilocumab) (84), and ELIPSE study (evinacumab) (5).

B.2.9.3.2 Patient selection

Cuchel *et al.* (2013) was a multicentre trial that enrolled patients from several countries. The diagnostic criteria for HoFH were based either on clinical criteria (history of untreated total cholesterol >13 mmol/L and triglycerides <3.4 mmol/L and both parents with history of

untreated total cholesterol >6.5 mmol/L) or on documented mutation(s) in both alleles of the LDL receptor or of other genes known to affect LDL receptor function. Exclusion criteria included major surgery in the previous three months, congestive heart failure, history of liver disease or transaminases greater than two times the upper limit of normal (ULN), serum creatinine >221 μmol/L, recent malignancy, alcohol or drug abuse, known bowel disease or malabsorption, or chronic lung disease.

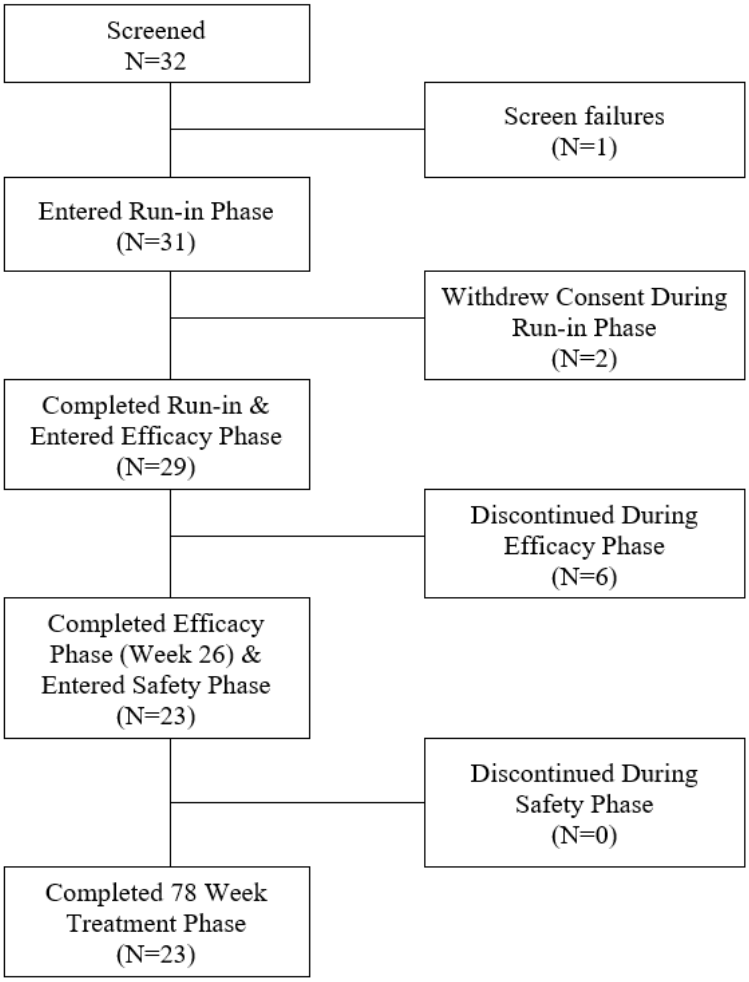
The authors did not report the method they used to select patients. Usually for a single-armed trial consecutive enrolment would be preferred, with all patients being systematically included if they met the inclusion criteria; however, it was not clear if that were the case for this study. This gives the rise to a material concern about selection bias. For RCTs, concerns about selection bias can be somewhat abated through randomisation and by comparing the baseline characteristics of the participants between groups (137), however, this is not possible with single-armed studies.

B.2.9.3.3 Patient attrition

A relatively large proportion of patients dropped out the study by Cuchel *et al.* (2013) (87), illustrated in Figure 22Figure 22. Patient flow in lomitapide pivotal trial (87). Two patients dropped out during the run in phase, whilst a further 6 patients dropped out during the treatment phase. The authors reported that all the discontinuations occurred during the efficacy phase, with the first discontinuation occurring 4 days after enrolment and the last at Week 22. Four discontinuations were due to AEs (3 were gastrointestinal [GI] events and 1 was headache); 1 was withdrawn for non-compliance with the protocol; and 1 withdrew consent for personal reasons. Further information was not reported.

Six discontinuations, with 23 completions, represented a withdrawal rate of 21%, with this increasing to 26% if the 2 patients who withdrew during the run-in phase are included. Conventionally, loss to follow up of more than 20% in an RCT is regarded as a serious issue, with Ferreira and Patino (2019) commenting “losses to follow-up of 20%, for example, can result in serious biases and, therefore, should not be considered acceptable” (141).

Figure 22. Patient flow in lomitapide pivotal trial (87).



B.2.9.3.4 Analysis datasets

The protocol specified the primary outcome was to be reported using ITT analysis (NCT00730236) (108), which is usually a suitable approach for data analyses in RCTs (137). Missing data, including from patients who discontinued the study, were imputed using a "missing-at-random" assumption. Analyses were conducted in which missing data were imputed using the last observation carried forward (LOCF) method. This was probably not appropriate, because the missing data was not "at random". This is a term that is usually applied to drop out or loss to follow up in trials that cannot be reasonably controlled for, such as true loss to follow up. However, in this case discontinuation was related to adverse events and adherence, so was not at random. Whilst the LCOF method of imputation has been described as specious (142), it would have reflected the dilution in efficacy due to treatment failure. However, instead in the published study (87) the authors reported the primary outcome as per protocol (PP) analysis, which does not account for treatment failure.

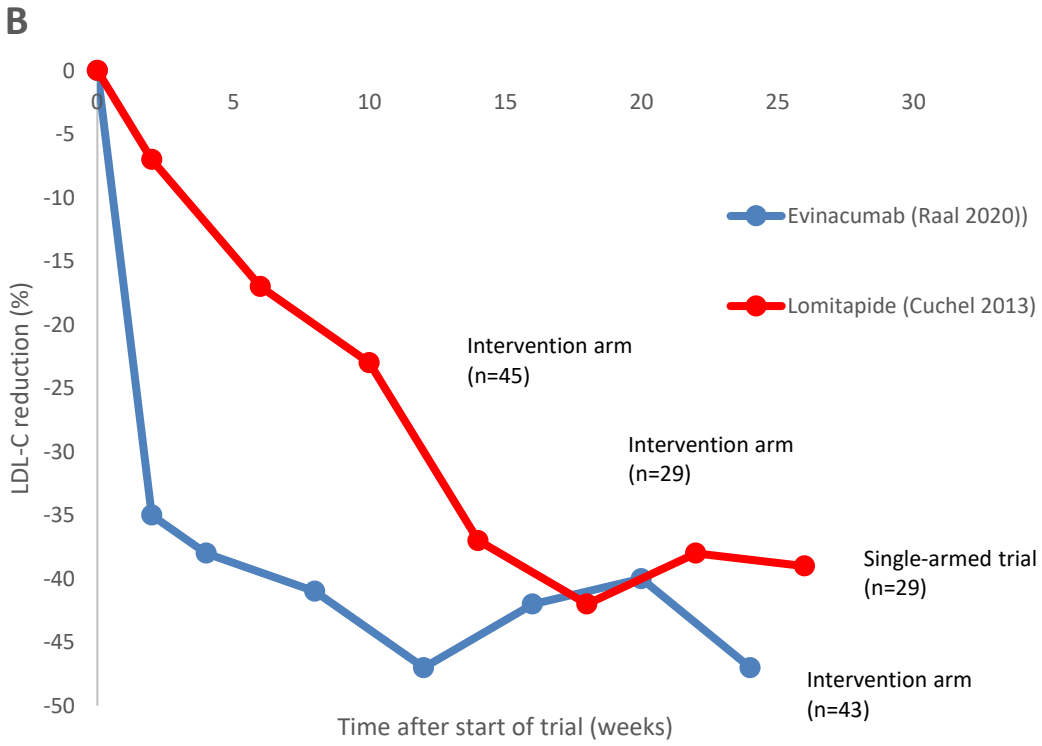
In contrast to the pivotal trial on lomitapide, the ELIPSE trial reported in the double-blind phase that there were no discontinuations in either arm of the study following randomisation,

thus the ITT, modified ITT (mITT), and PP groups were equivalent (5). Furthermore, [redacted] completed the 24-week open-label-extension treatment period, with [redacted].

B.2.9.3.6 Results

The primary outcome was change in LDL-C levels at 26 weeks, measured using a mixed linear model with imputed values for missing data assuming missing at random. Since this was a single-armed trial, the change from baseline was measured, rather than a comparison with placebo. The authors reported there was a fall in LDL-C over this time period of -50% (95% CI -62% to -39%, p<0.001) using PP analysis (n=23). However, the authors also presented a graph showing the fall in LDL-C levels associated with lomitapide over time (up to 26 weeks) using the ITT dataset. This is compared with the longitudinal data reported from the ELIPSE RCT in Figure 23. The ITT primary endpoint for lomitapide was also reported in the trial protocol (108).

Figure 23. Longitudinal efficacy of lomitapide compared with evinacumab using intention-to-treat data (reduction from baseline).



Abbreviations: LDL-C, low-density lipoprotein cholesterol.

It can be seen from this graph that reductions in LDL-C associated with lomitapide are gradual until about 12 weeks, when the values plateau. At 26 weeks, the timepoint of the primary outcome, the LDL-C change was reported as -40.1% (95% CI -51.5% to -28.7%) using ITT analysis (108).

Longer-term data on lomitapide was reported in an extension study that followed up patients from the pivotal trial for up to 294 weeks (107). The authors reported a change of LDL-C of -45.5% (95% CI -61.6% to -29.4%, P<0.001) from baseline at 126 weeks. However, particular care should be taken when interpreting these data, as the number of patients contributing data materially decreased over time, highlighting the possibility of attrition bias. Furthermore, even during the pivotal trial phase, only 19 patients contributed to the data, fewer than the 23 patients who were previously reported to have completed this study.

B.2.9.3.7 Critical appraisal

Critical appraisal was conducted on this study using the Newcastle Ottawa scale (110) where it was judged to be at high risk of bias (Appendix D.4, Table 15). Additional assessment using the ROBINS-I tool (143), recommended by the Cochrane collaboration (137), found that the trial was at serious risk of bias (Appendix D.4, Table 14). However, it should be noted neither of these two tools were designed to assess risk of bias or confounding in single-armed studies.

B.2.9.4 Matched adjusted indirect comparison (MAIC) with lomitapide

As an anchored comparison between evinacumab and lomitapide was not possible because the lomitapide data were single-armed, a matched adjusted indirect comparison (MAIC) was undertaken. This is a non-parametric likelihood reweighting method which allows the propensity score logistic regression model to be estimated without patient level data (PLD) in one of the treatment arms (144). In this case, individual evinacumab-treated participants were assigned statistical weights that adjust for their over or under-representation relative to the average prognostic factors and treatment effect modifiers observed in each comparative evidence source. These weights are then incorporated into the analyses.

B.2.9.4.1 Selection of efficacy dataset

The efficacy data selected for lomitapide were from the ITT dataset, as reported in the published protocol of the pivotal lomitapide trial (108), and not the PP data reported by Cuchel *et al.* (2013) (87). The use of ITT data is preferred over PP data by HTA assessors and agencies (137, 145-147), including NICE (148).

The efficacy data for evinacumab were derived from the full dataset matched to the identified prognostic factors. Note that in the ELIPSE trial, ITT and PP datasets were equivalent.

B.2.9.4.2 Selection of prognostic factors and effect modifiers

The following prognostic factors were identified from a combination of clinical inputs identified by clinical experts and through assessment of the evidence base, including IPD analysis of the ELIPSE trial (see Appendix D.2.4.2 for further details): age (from the clinical input), history of CHD (from the clinical input and assessment of the evidence base), and LDL-C (from the clinical input). LDL-R mutation status defective/defective or null/null (from clinical input) were considered to be potential prognostic factors but were not reported by Cuchel *et al.* (2013), so could not be applied. Therefore, matching was restricted to age, history of CHD, and baseline LDL-C levels only (Appendix D.2.4.2). As an additional

sensitivity analyses, matching was performed using the age criteria only, and on the ELIPSE population with the patients' receiving concomitant lomitapide removed.

B.2.9.4.3 Results of MAIC

The results of the matching are presented in Table 21. In the main analysis, when all the matching variables were applied, the estimated sample size (ESS) of the evinacumab weighted cohort was 9.9. This increased to 23.6 when only age was applied as a matching factor. This suggests the weights are highly variable due to limited population overlap between the ELIPSE and Cuchel *et al.* (2013) in terms of prior CHD and baseline LDL-C levels, and that the estimate may be unstable. The ESS decreased to 3.9 when patients receiving lomitapide were excluded.

The results of the MAIC of evinacumab compared with lomitapide are reported in Table 21. In the base case MAIC, evinacumab was associated with a larger change in LDL-C than lomitapide, with an additional change of -5.08% (mean difference). This change was -6.40% (95% CI -20.56% to 7.76%) when only age was controlled for. Neither of these differences were statistically significant. The low ESS in the cohort with lomitapide patients excluded meant meaningful analysis was not possible (see Appendix D.2.5).

Table 20. Comparison of baseline characteristics before and after matching to Cuchel *et al.* (2013).

Cohort	n/ESS	Age (years), mean	CHD (% yes)	LDL-C (mg/dL), mean
Evinacumab unadjusted	43.0	44.3	51.0	259.5
Main analysis (matching variables: age, CHD, LDL-C)				
Evinacumab weighted	9.9	30.7	72.0	336.4
Lomitapide	29.0	30.7	72.0	336.4
Sensitivity analysis (matching variable: age)				
Evinacumab weighted	23.6	30.7	NA	NA
Lomitapide	29.0	30.7	NA	NA

Abbreviations: CHD, coronary heart disease; dL, decilitre; ESS, effective sample size; LDL-C, low-density lipoprotein cholesterol; mg, milligram; n, sample size; NA, not applicable.

Table 21. Results of the MAIC of evinacumab vs. lomitapide.

Method	Matching variables	Evinacumab n/ESS	Lomitapide n	Mean (95% CI) evinacumab	Mean (95% CI) lomitapide	Mean Difference (95% CI) evinacumab vs lomitapide
Including patients receiving lomitapide						

Unadjusted Naïve ITC	NA	43.0	29.0	-47.24 (-56.18 to -38.31)	-40.1 (-51.47 to 28.73) [a]	-7.14 (-21.91 to 7.63)
MAIC	Age, CHD, LDL-C	9.9	29.0	-55.08 (-71.90 to -38.27)	-40.1 (-51.47 to 28.73) [a]	-14.98 (-36.76 to 6.80)
MAIC (sensitivity analysis)	Age	23.6	29.0	-56.40 (-64.66 to -48.14)	-40.1 (-51.47 to 28.73) [a]	-16.3 (-30.72 to -1.88)*

Abbreviations: CHD, coronary heart disease; CI, confidence interval; ESS, effective sample size; ITC, indirect treatment comparison; LDL-C, low-density lipoprotein cholesterol; MAIC, matching-adjusted indirect comparison; n, number of patients.

[a] Data presented to no decimal places to reflect the reporting style by Cuchel *et al.* (2013).

*Evinacumab was statistically superior to lomitapide when the evinacumab cohort was matched for age.

B.2.9.4 Matched indirect comparison with ezetimibe (background treatment)

Due to the nature of the RCT data reported on ezetimibe, which was not placebo-controlled (75), it was necessary to use an unanchored MAIC using the same methodology as that used for the lomitapide comparison. The ESS was for evinacumab in the base case analysis was 22.3 and it was 25.5 in the sensitivity analysis (adjusted for age only). The mean differences were -26.46 (95% CI -39.80 to -13.13) for the naïve comparison, -34.35 (95% CI -46.06 to -22.64) for the base case analysis, and -36.16 (95% CI -47.27 to -25.05). All these differences were statistically significant in favour of evinacumab.

B.2.9.5 Bucher comparison with evolocumab (background treatment)

The TESLA B study was a parallel RCT with many methodological similarities to the ELIPSE study. Because both studies used placebo as a comparator, it was considered suitable for a Bucher ITC (149) (Appendix D.2.6). In its simplest form, a Bucher ITC compares results from two separate RCTs through a common comparator, maintaining the randomization between treatments in each study. There is no requirement for analysis of IPD and no adjustments for covariates are considered necessary.

Only the change in LDL-C levels at 12 weeks could be analysed because other data, such as the proportion of people with a 50% reduction in LDL-C, were not reported in the TESLA B study (as evolocumab lacked the efficacy to achieve this). There was a -55.23% change compared with baseline associated with evinacumab (95% CI -74.41% to -36.04%), compared with a -30.9% (95% CI -43.9% to -18.0%) change for evolocumab, resulting in a mean difference of -24.33% (95% CI -47.50% to -1.15%). This difference was significant in favour of evinacumab.

B.2.9.6 Limitations of the ITC

The MAIC reported no statistically significant difference in clinical effectiveness between evinacumab and lomitapide in terms of LDL-C reduction, with wide confidence intervals observed. However, a qualitative comparison reported that lomitapide was associated with

more frequents AEs, SAEs, and treatment discontinuations. The inferences than can be made from ITC analyses are restricted by the methodological limitations and reporting quality of the informing studies. As the key comparator was lomitapide, particular attention needs to be drawn to the limitations of the pivotal trial in terms of its efficacy, which are discussed fully in Section B.2.9.3 Pivotal study on lomitapide (Cuchel *et al.* 2013)

The informing study for lomitapide was single-armed and thus required comparison using an unanchored MAIC (144). A key element of MAIC is to use propensity-matching to control for known confounders, such as prognostic factors or treatment effect modifiers, in the index trial using IPD analyses. However, there are two important drawbacks to using MAICs in this way. Firstly, the MAIC will naturally transform the efficacy data to match the comparator population (as there is no IPD for available for this) rather than the intervention (150), as would be preferred for purposes of the CEM. Secondly using this methodology effectively reduces the sample size of the intervention group, which reduces the power of analysis. In this case, as the intervention arm of the ELIPSE trial was relatively small (n=43), the effect of controlling for the three identified confounders that were reported in the lomitapide study (age, history of CHD, and baseline LDL-C) reduced the ESS to 9.9, which was slightly below the usual threshold acceptable for this unanchored analysis type (<10 patients). This meant the results were subject to considerable uncertainty and were potentially unstable, which impacts on how the results should be used viewed (i.e., with caution).

Whilst HoFH is a rare disease, the standard of care has changed rapidly in recent years, with the development of statins and ezetimibe, and latterly lomitapide and PCSK9 inhibitors. This is reflected in the publication dates of the studies included in the ITC and MAICs, which spanned 18 years, ranging from 2002 for ezetimibe (75); 2013 for lomitapide (87); 2015 for evolocumab (78); and 2020 for evinacumab (5). Because each of these interventions has reported clinically significant efficacy benefits in their respective trials, they have been retained in later studies as background treatments, with discontinuation being both impractical and probably unethical. That is, trials of new drugs tend to be *additive* to standard of care, rather than replacing an element of it. For instance, the ELIPSE trial enrolled patients who were stabilised on optimal treatment (all modalities), and this background treatment was continued concomitantly throughout the trial (5).

However, a major limitation of the current analysis was that the sample size was insufficient to allow for propensity matching adjustment to account for background treatment, which also included the comparator of interest (i.e., lomitapide itself) in 14/65 (21.5%) of patients in ELIPSE. Additionally, the proportion of patients receiving apheresis were different in each trial, ranging from 62% in the lomitapide study (87); around 50% in the ezetimibe study (75); 33% in ELIPSE (5); whilst it was an exclusion criteria in TESLA B (evolocumab) (78). Both background LDL apheresis and pharmacological interventions would be expected to have a substantial impact on LDL-C levels, and thus confound the interpretation of results. Similar issues applied to the Bucher ITC comparing evinacumab with evolocumab, because around 80% of patients in the ELIPSE trial (5) received a PCSK9 inhibitor, the comparator of interest in TESLA B (78). However, anchored ITCs assume the distribution of interactions between relative treatment effects and covariates is balanced between trials (151); however, this was unlikely to be the case in this ITC.

In summary, although the efficacies of evinacumab and lomitapide were not statistically different (whether adjusted or naïve data were compared), evinacumab was numerically

superior, and this difference was not trivial from a clinical perspective. In all analyses undertaken, evinacumab was clearly superior to the background treatments of evolocumab or ezetimibe (the latter of which is used relatively ubiquitously in patients with HoFH). The studies on the interventions for the treatment of HoFH were limited by factors relating to study design, quality of reporting, and small sample sizes. Syntheses of these studies in the form of ITC and MAICs are further impeded by issues with study heterogeneity in terms of population and especially background treatment, as well as insufficient sample sizes which are needed to control for this. This was particularly true for the lomitapide pivotal trial. Future head-to-head trials are unlikely to address these issues due to the difficulties associated with the low disease prevalence and concerns regarding clinical equipoise.

Nevertheless, these measures of relative efficacy were considered to represent the best comparative estimates available from the current published studies, and as a result were used to inform the base case of the CEM. Alternate estimates of efficacy using naïve data are presented in scenario analysis. For the efficacy of lomitapide, as there was a discrepancy between the planned (108) and published (87) results for lomitapide, the ITT efficacy was selected as it was considered to be more robust and matched the authors *a priori* analysis plan. Additionally, the use of ITT data is recommended by NICE (148). Nonetheless, the following provisos and caveats should be considered relating to the use of ITC and overall evidence limitations:

1. As evinacumab was assessed in a high-quality RCT considered to be at low risk of bias, there is considerably more confidence in the evinacumab results than the lomitapide results (Section B.2.9.3 Pivotal study on lomitapide (Cuchel *et al.* 2013)
2. The large relative reduction in LDL-C levels observed by evinacumab are particularly impressive considering they were *additional* to optimal use of all applicable background therapy, bearing in mind the diminishing returns that might be expected with decreasing baseline LDL-C and increasing usage of concomitant treatments
3. The absolute change in LDL-C was similar for evinacumab (-3.43 mmol/L [95% CI -4.53 mmol/L to -2.30 mmol/L]) compared with lomitapide, using ITT data (-3.49 mmol/L), despite the baseline LDL-C levels being higher in the pivotal lomitapide trial. It was also observed that the relative change in LDL-C levels associated with evinacumab was slightly higher when lomitapide patients were removed in subgroup analysis (-50.9%) (127), and it would be expected that evinacumab would have a greater absolute effect in populations naïve of various background treatments (due to increased LDL-C baseline levels)
4. Finally, the efficacy of evinacumab should be viewed in the broader context of its good safety profile and its suitability for use in all people with HoFH, regardless of underlying mutation status, and including adolescent patients

B.2.10 Adverse reactions

Summary

- Evinacumab was well-tolerated in the ELIPSE trial, with a similar number (no statistical difference) of TEAEs associated with the drug and placebo in the DBTP. Two SAEs that occurred in the evinacumab group were adjudicated to not be related to the drug.
- In the OLTP, a total of 47 patients (73%) experienced at least 1 TEAE. These were transient and mild in nature, with no patient experiencing a TEAE leading to death or discontinuation of study treatment.
- [redacted]
- No SAEs were identified that were associated with evinacumab in the single-armed R1500-CL-1331 trial.
- [redacted]

B.2.10.1 ELIPSE trial (DBTP)

A total of 29 patients (65.9%) in the evinacumab treatment group and 17 patients (81.0%) in the placebo treatment group experienced at least 1 TEAE (Table 22). No patients experienced a TEAE leading to death or discontinuation of study treatment. Two patients (4.5%), both in the evinacumab treatment group, experienced 1 serious TEAE (SAE) each.

Table 22. Overview of Adverse Event Profile: TEAEs During the DBTP (Safety Analysis Set).

	Placebo IV Q4W (n=21)	**Evinacumab 15 mg/kg IV Q4W (n=44)**
Patients with any TEAE	17 (81.0%)	29 (65.9%)
Patients with at least one serious TEAE	0	2 (4.5%)
Patients with at least one TEAE resulting in discontinuation of treatment	0	0
Patients with any TEAE resulting in death	0	0

Abbreviations: DBTP, double-blind treatment period; IV, intravenous; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event.

Data from Raal *et al.* (2020) (5).

Treatment-emergent SAEs were adjudicated to have occurred in 2 (4.5%) patients (both in the evinacumab group) and were reported as urosepsis and suicide attempt, neither of which was considered related to the study drug, with both patients fully recovering (5). A summary of all the TEAEs reported in the ELIPSE trial is presented in Table 23.

A total of 5 patients (11.4%) in the evinacumab treatment group and 1 patient (4.8%) in the placebo treatment group experienced a TEAE classified by the investigator as related to study treatment. In the evinacumab treatment group, the treatment-related TEAEs were infusion site pruritus and nasopharyngitis (2 patients each), and pyrexia, gastroenteritis, muscular weakness, epistaxis, upper respiratory tract inflammation, and vascular pain (1 patient each). One patient in the placebo group had treatment-related TEAEs of face oedema and infusion site hypoaesthesia.

During the DBTP, there were no suspected major adverse cardiovascular events reported (5).

Table 23. Summary of TEAEs in ELIPSE trial (DBTP).

	Placebo IV Q4W (n=21)	**Evinacumab 15 mg/kg IV Q4W (n=44)**
Patients with any TEAE, n (%)	17 (81.0)	29 (65.9)
Nasopharyngitis	5 (23.8)	7 (15.9)
Influenza-like illness	0	5 (11.4)
Headache	5 (23.8)	4 (9.1)
Rhinorrhoea	0	3 (6.8)
Gastroenteritis	0	2 (4.5)
Infusion-site pruritus	0	2 (4.5)
Pyrexia	1 (4.8)	2 (4.5)
Cough	0	2 (4.5)
Dental caries	0	2 (4.5)
Diarrhoea	1 (4.8)	2 (4.5)
Dyspepsia	0	2 (4.5)
Toothache	2 (9.5)	2 (4.5)
Dizziness	0	2 (4.5)
Patients with at least one SAE, n (%)	0	2 (4.5)
Urosepsis	0	1 (2.3)
Suicide attempt	0	1 (2.3)
Patients with at least one TEAE resulting in discontinuation of treatment, n (%)	0	0
Patients with any TEAE resulting in death, n (%)	0	0

Abbreviations: DBTP, double-blind treatment period; IV, intravenous; Q4W, once every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Data from Raal *et al.* (2020) (5).

B.2.10.2 ELIPSE trial (OLTP)

Safety was assessed in all 64 patients of the OLTP SAF, which was comprised of 44 patients who had already received evinacumab in the DBTP of this study (the double-blind evinacumab treatment group) and 20 patients who had previously received placebo in the DBTP of this study and switched to OL evinacumab in the OLTP (the double-blind placebo treatment group).

[redacted]

Table 24. Number (%) Patients with TEAEs that occurred in ≥2 patients (Total Evinacumab) by Primary System Organ Class.

Organ system	TEAEs reported	DB Evinacumab 15 mg/kg IV Q4W (n=44)	DB Placebo IV Q4W (n=21)	Total (n=64)
All	**Patients with any TEAE, n (%)**	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	Any	[redacted]	[redacted]	[redacted]
	Nausea	[redacted]	[redacted]	[redacted]
	Toothache	[redacted]	[redacted]	[redacted]
General disorders and administration site	All	[redacted]	[redacted]	[redacted]
	Asthenia	[redacted]	[redacted]	[redacted]
	Influenza like illness	[redacted]	[redacted]	[redacted]
Immune system disorders		[redacted]	[redacted]	[redacted]
Infections and infestations	All	[redacted]	[redacted]	[redacted]
	Nasopharyngitis	[redacted]	[redacted]	[redacted]
	Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	All	[redacted]	[redacted]	[redacted]
	Back pain	[redacted]	[redacted]	[redacted]
	Muscle spasms	[redacted]	[redacted]	[redacted]
Nervous system disorders	All	[redacted]	[redacted]	[redacted]
	Headache	[redacted]	[redacted]	[redacted]
All	**Patients with at least one serious TEAE, n (%)**	[redacted]	[redacted]	[redacted]
All	**Patients with at least one TEAE resulting in discontinuation, n (%)**	[redacted]	[redacted]	[redacted]
All	**Patients with any TEAE resulting in death, n (%)**	[redacted]	[redacted]	[redacted]

Abbreviations: DB, double-blind; IV, intravenous; OLTP, open-label treatment period; Q4W, once every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Data on file.

B.2.10.3 Study R1500-CL-1719 (long-term safety and efficacy)

Over the course of R1500-CL-1719 [redacted]

Table 25. Summary of TEAEs related to treatment that occurred during R1500-CL-1719.

Organ system/description	TEAEs reported (preferred term)	New evinacumab (n=44)	Continue evinacumab (n=70)	Total evinacumab (n=116)
All	**Patients with any TEAE, n (%)**	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	Any	[redacted]	[redacted]	[redacted]
	Oral pigmentation	[redacted]	[redacted]	[redacted]
General disorders and administration site	All	[redacted]	[redacted]	[redacted]
	Asthenia	[redacted]	[redacted]	[redacted]
	Feeling hot	[redacted]	[redacted]	[redacted]
	Infusion site erythema	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	Any	[redacted]	[redacted]	[redacted]
	Hepatic function abnormal	[redacted]	[redacted]	[redacted]
Infections and infestations	Any	[redacted]	[redacted]	[redacted]
	Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Investigations	Any	[redacted]	[redacted]	[redacted]
	Blood glucose increased	[redacted]	[redacted]	[redacted]
	Transaminases increased	[redacted]	[redacted]	[redacted]
	Any	[redacted]	[redacted]	[redacted]

Organ system/description	TEAEs reported (preferred term)	New evinacumab (n=44)	Continue evinacumab (n=70)	Total evinacumab (n=116)
Musculoskeletal and connective tissue disorders	Muscle spasms	[redacted]	[redacted]	[redacted]
Nervous system disorders	All	[redacted]	[redacted]	[redacted]
	Headache	[redacted]	[redacted]	[redacted]
	Hypoaesthesia	[redacted]	[redacted]	[redacted]
	Paraesthesia	[redacted]	[redacted]	[redacted]
Skin and subcutaneous disorders	Any	[redacted]	[redacted]	[redacted]
	Acne	[redacted]	[redacted]	[redacted]
	Pruritus	[redacted]	[redacted]	[redacted]
	Swelling face	[redacted]	[redacted]	[redacted]

Abbreviations: TEAE, treatment-emergent adverse event.

A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.

B.2.10.3 Study R1500-CL-1331 (proof-of-concept)

In general, evinacumab was well tolerated during the main study period and throughout the open-label extension period (11). All 9 patients experienced at least 1 TEAE (data on file). The most frequently reported TEAEs were nausea (4 patients), back pain (4 patients), nasopharyngitis (2 patients), and musculoskeletal pain (2 patients). There were no deaths and no TEAEs that led to treatment discontinuation during the study (11).

Three patients experienced SAEs during the study, none of which were considered related to the study drug or study procedures. The SAEs included 1 case of coronary artery disease, 1 case of coronary artery stenosis, and 1 case of bronchospasm due to known food allergy. Six drug-related TEAEs were reported, 2 of which were injection-site reactions of mild severity, 1 was myalgia of moderate severity, 2 were hot flush of mild severity, and 1 was epistaxis classified as severe.

B.2.10.4 Other studies

Rosenson *et al.* (2020) reported on a phase 2 trial that investigated the efficacy and safety of subcutaneous and IV evinacumab compared with placebo in patients with refractory hypercholesterolemia who had been treated with maximum tolerated doses of statins and other LLT, including a PCSK9 inhibitor (152). Of the 272 people randomised, 28 received IV evinacumab at 15 mg/kg every 4 weeks (recommended regimen for HoFH) (1), 35 people received IV evinacumab at 5 mg/kg every 4 weeks, and 33 people received IV placebo every 4 weeks. There were no significant differences between groups in terms of overall AEs, and

no deaths reported in any of the arms. The only AE that was considered to be due to evinacumab and required discontinuation was anaphylaxis following the second dose in the 15 mg/kg group, with the patient making a full recovery. The AEs reported in this study are reported in Table 26.

Table 26. Adverse events associated with evinacumab in phase 2 study reported by Rosenson *et al.* (2020).

	Evinacumab 15 mg/kg IV Q4W (n=37)	**Evinacumab 15 mg/kg IV Q4W (n=36)**	**Placebo IV Q4W (n=33)**
Any AE	31 (84%)	27 (75%)	23 (70%)
≥ 1 SAE	6 (15%)	2 (6%)	1 (3%)
≥1 Adverse Event Resulting in Treatment Discontinuation	2 (5%)	2 (6%)	1 (3%)
Any Adverse Event Resulting in Death	0 (0%)	0 (0%)	0 (0%)
Abbreviations: AE, adverse event; IV, intravenous; Q4W, once every 4 weeks; SAE, serious adverse event.			

B.2.10.5 Adverse events of special interest

B.2.10.5.1 Liver function

[redacted].

B.2.10.5.2 Hypersensitivity reactions

[redacted].

B.2.10.5.3 Immunogenicity

[redacted]

Table 27. Anti-drug antibody status (and category) and neutralising antibody status for total population.

ADA Status/Category NAb Status	New evinacumab (n=46)	Continue evinacumab (n=70)
ADA status		

Negative	[redacted]	[redacted]
Pre-existing immunoreactivity [a]	[redacted]	[redacted]
Treatment boosted response [b]	[redacted]	[redacted]
Treatment-emergent response [c]	[redacted]	[redacted]
NAb status		
Negative	[redacted]	[redacted]
Positive	[redacted]	[redacted]

Abbreviations: ADA, anti-drug antibody; NAb, neutralising antibody.

[a] Pre-existing immunoreactivity defined as a positive ADA assay response at baseline, with all post-first dose ADA results negative, or a positive assay response at baseline, with all post-first dose ADA assay responses less than 9-fold over baseline titre levels. For patients who participated in a previous study (R1500-CL-1331 or R1500-CL-1629), the baseline ADA status in the parent study was considered the baseline ADA status of the patient.

[b] Treatment boosted defined as any post-first dose ADA response that is at least 9-fold over baseline titre levels when baseline results are positive.

[c] Treatment-emergent defined as any post-first dose ADA positive response when baseline results are negative or missing. Both cases identified were categorised as transient, defined as defined as not persistent or indeterminate (i.e., no positive consecutive results.

B.2.10.5.4 TEAEs resulting in dose reductions or discontinuation

[redacted].

B.2.11 Ongoing studies

The long-term safety and efficacy study R1500-CL-1719 (NCT03409744) is ongoing (121), with interim data being presented in this submission (see Table 11). The study was completed on April 13th 2023 (153). No other ongoing studies of evinacumab in this population have been identified. A study of evinacumab in children with HoFH (R1500-CL-17100) (153) has recently completed but is out of scope of the decision problem.

In collaboration with patient advocacy group, FH Europe, a study is currently ongoing to further explore the impact of HoFH on QoL. The aim of this study is to capture QoL outcomes in people with HoFH across multiple countries in Europe, including the UK. Data will also be collected from informal caregivers. As well as capturing broad QoL data, the study measures overall disease burden from HoFH and productivity loss to society associated with current treatment approaches. Initial data will be available in June 2023 with the final data expected to be published in Q4 2023/Q1 2024.

B.2.12 Interpretation of clinical effectiveness and safety evidence

HoFH is an ultra-rare disorder with a heterogeneous presentation, and as such, investigating the safety and efficacy of interventions for the condition is inherently challenging. Evinacumab has been studied in a phase 3 placebo-controlled study (R1500-CL-1629, ELIPSE) (5) that has been assessed as being of high methodological quality and at low risk of bias (Section B.2.5 Critical appraisal of the relevant clinical effectiveness evidence). This study was designed to be pragmatic, enrolling patients who were representative of those on current management pathways and receiving optimal individualised treatment. In the absence of clinical cardiovascular outcomes which were not feasibly detectable in this population (due to small sample sizes and limited timeframes), the ELIPSE study reported intermediate endpoints (in particular, circulating LDL-C levels) that fully reflected the benefits of treatment. The ELIPSE RCT provides robust evidence supporting the adoption of evinacumab and represents some of the strongest experimental evidence for any intervention in the management of HoFH. Patients from the ELIPSE study, as well as an intake of evinacumab naïve patients, contributed to the long-term safety and efficacy study (R1500-CL-1719) [redacted] (121).

The ELIPSE trial has unequivocally demonstrated the efficacy of evinacumab in people with HoFH. This study reported an approximate change from baseline of -50% in circulating LDL-C levels, beyond that which can be achieved in addition to current therapy, including with LDL apheresis (5). In absolute terms, the changes were -3.42 mmol/L (95% CI -4.53 mmol/L to -2.30 mmol/L), or -132.1 mg/dL (95% CI, -175.3 mg/dL to -88.9 mg/dL, P<0.001). Reductions in LDL of this magnitude will undoubtedly lead to large, clinically significant reductions in CVD and its attendant consequences on an individual's health, HRQoL, and life-expectancy (26). Furthermore, this reduction is maintained for [redacted]. Evinacumab has also demonstrated a favourable safety profile, with no directly recognised deaths or AEs necessitating discontinuation or dose reduction of the drug in published studies in people with HoFH. Evinacumab shows no specific toxicity to any organ system, and TEAEs that have been attributed to the drug on adjudication have been generally mild in severity and reversible (121).

Evinacumab represents a new target class of drugs, and its mechanism of action, inhibition of ANGPTL3, is novel and independent of pharmacological pathways absent in null/null or negative/negative patients. The ELIPSE RCT demonstrated that all enrolled patients benefitted from a similar relative reduction in LDL-C levels following treatment with evinacumab, regardless of their genotypic or phenotypic presentation (5). This is of paramount importance for the most severely affected patients who have minimal LDLR function, and for whom meaningful response is only gained through LDLR-independent LDL-C lowering mechanisms. The unique mechanism of action of evinacumab also means it is effective *in addition* to current treatments. This was proven in the ELIPSE trials where the therapeutic benefit of evinacumab was observed regardless of background or concomitant treatments used (5).

Current treatments for HoFH do not address patients' needs. Many of the existing pharmacological treatments for HoFH have limited efficacy in general, and particularly so in those with the most severely affected genotypes. The use of polypharmacy may be limited by drug-drug interactions, particularly with statins (68, 69), which may effectively contraindicate these drugs in some patients with HoFH. Statins and PCSK9 inhibitors such as evolocumab have greatly reduced efficacy in patients with severe LDLR mutations. Ezetimibe has limited efficacy (75) and its mechanism may also be partly dependent on the upregulation of LDLR (154), thus its efficacy is limited in patients with HoFH.

If, as is usually the case, treatment with statins, ezetimibe, and PCSK9 inhibitors do not adequately achieve target levels, lomitapide is currently the only other pharmacological option available for the treatment of HoFH (20). However, the evidence for lomitapide is limited to single-armed data (see Section B.2.9.3 Pivotal study on lomitapide (Cuchel *et al.* 2013) meaning there is considerable uncertainty concerning its true efficacy. The principal practical limitation of lomitapide is related to its mechanism of action, which inevitably leads to a dose-related accumulation of hepatic fat with attendant AEs. Effective use of lomitapide requires life-long adherence to a strict low-fat diet which may not be sustainable over the longer-term for some people. Non-compliance with a low-fat diet may exacerbate GI-mediated AEs. Combined, these factors can diminish compliance with the drug, leading to cessation which impacts the efficacy of lomitapide seen in the real-world (86). Accumulation of hepatic fat has potentially serious consequences for long-term health (135) and thus continued monitoring of patients receiving the drug, including frequent LFTs and liver imaging, are required (6). Lomitapide is also an inhibitor of the metabolic enzyme CYP3A4, and so has the potential to interact with other drugs, such as statins, requiring dose changes and additional monitoring from healthcare practitioners (155). Lomitapide is not suitable for use in people aged <18 years and so cannot be used early in the process of preventing atherosclerosis, leaving a significant unmet need in younger people with HoFH.

LDL apheresis is the principal non-pharmacological method of treating HoFH and is thought to achieve time average changes in LDL-C of between -40% to -30% (95). However, LDL apheresis typically requires sessions at least once every 2 weeks, with associated risks of AEs related to arteriovenous access, and has been linked with an iatrogenic mediated loss in health-related quality of life (HRQoL) (46). The requirement for administration in specialist centres may also cause issues with respect to geographical inequality. Because LDL apheresis can be a drain on healthcare resources and represents a significant opportunity cost, some clinicians now recommend it only as last-line treatment once all available pharmacological treatments have been used (57). The reality in the management of HoFH is, due to the issues discussed above, LDL apheresis or lomitapide alone or in combination are not usually enough to reduce LDL-C to target levels, and will leave patients at persistent high risk of premature CVD (2). Evinacumab can be used to address these unmet needs and effectively treat nearly all people with HoFH, regardless of their underlying mutation and background treatment. There are no contraindications to evinacumab other than hypersensitivity to the active ingredient or excipient (1). Evinacumab has a favourable safety profile, which has enabled its authorisation for use in adolescents (≥12 years) (1), which may be extended to paediatric populations (153). Adoption of evinacumab into UK practice is therefore urgently needed and entirely justified for this population.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A literature review using systematic methodology was undertaken to identify and summarise the best available cost-effectiveness evidence for evinacumab and relevant comparator therapies for the treatment of HoFH. The original search was undertaken on 15 October 2020, with an updated search undertaken on 23 February 2022, and a further updated search undertaken on 13 March 2023. Full details of the methodology of the searches are reported in Appendix G. No relevant cost-effectiveness studies in this disease area were identified.

B.3.2 Economic analysis (de novo model)

Summary

- A de novo cost-effectiveness model was developed that was consistent with the NICE reference case. This was a state-transition decision-analytic model that simulated patients with HoFH experiencing CV events over the perspective of a lifetime.
- Patient baseline characteristics were principally derived from the ELIPSE trial (5). Base line CV risk were modelled using fitted data derived from a retrospective observational study of patients from the UK and South Africa (156). These were mapped to CV events using data from the general population (157).
- The efficacy of all treatments (background, intervention or comparator) was derived from an ITC (Section B.2.9 Indirect and mixed treatment comparisons). LDL-C levels were used as a surrogate endpoint for CV event reduction by applying data from a meta-analyses (23).
- Costs and utilities associated with health states were mainly derived from estimates used in previous models in this disease area (158).
- Uncertainties were tested using extensive one-way deterministic analysis, probabilistic sensitivity analysis, and scenario analysis. Results were presented as the incremental cost-effectiveness ration and net monetary benefit.

An economic evaluation was conducted to assess the cost-effectiveness of evinacumab in the treatment of adult and adolescent patients (≥12 years) with HoFH. A *de novo* economic model was developed in the absence of previously published cost-effectiveness models on interventions for the treatment of HoFH. In the model, evinacumab is used in addition to SoC as a third- or fourth-line treatment for HoFH and is anticipated to displace the use of lomitapide. The model applies estimated treatment effects to patients' baseline LDL-C concentration, which is then used to adjust their baseline risk of CV events.

B.3.2.1 Patient population

The economic model includes patients diagnosed with HoFH who have not achieved target LDL-C concentrations (1.8 mmol/L) on current LLTs including high-intensity statins, ezetimibe, evolocumab, and LDL apheresis (Section Abbreviations: CV, cardiovascular; HoFH, homozygous familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NMB, net monetary benefit.

B.3.3.2 Baseline characteristics). In the base case, the patient characteristics are based on the pivotal ELIPSE trial (5) as far as was practicable.

The patients' starting age in the model is 42 years, which is the mean age of patients in the ELIPSE trial. Patients are assumed to have a mean body mass index (BMI) of 25.6, mean body weight of 73kg, and 54% of patients are female. The proportion of patients with null/null mutation is assumed to be 32% in the base case, in line with the ELIPSE trial (5). The baseline LDL-C used in the model was derived from a UK-based retrospective registry (156). This registry was chosen as it provides a means of linking LDL-C concentration to the risk of CV events (Section B.3.3.3 Baseline CV event risk.

At baseline, patients are assumed all to be in a 'stable HoFH' health state without having previously experienced a major CV event. This health state is considered equivalent to stable angina with respect to healthcare resource use and HRQoL. This represents a limitation of the current evaluation, since a proportion of the eligible population will have experienced a previous major CV event (as was observed in the pivotal ELIPSE study cohort). However, the impact of this simplifying assumption on the modelled incremental outputs is expected to be minimal.

B.3.2.2 Model perspective

The perspective for this analysis is that of the NHS and Personal and Social Services in England and Wales in line with the NICE reference case. All costs are reported in GBP (£), reflecting the 2020 cost year.

B.3.2.3 Time horizon and discount rate

The base case analysis adopts a lifetime time horizon as stipulated by NICE guidelines (148, 159), and since HoFH is a lifelong, incurable chronic condition, the patients' age is capped at 100 years, and survival is not considered beyond this limit.

The cycle length is 1 year, and a half cycle correction is applied to all health state transitions. Costs and outcomes are discounted at the standard rate of 3.5% per annum, as per NICE guidance (148).

B.3.2.4 Model structure

A state-transition decision-analytic model (semi-Markov model) was developed to estimate the cost-effectiveness of evinacumab versus lomitapide in HoFH. State transition models are often used to model the natural history of chronic or long-term conditions using a set of mutually exclusive health states. Patients can be in only one state at each model cycle, and the time a subject spends within a state is weighted by health-state specific outcomes (e.g.,

health-related utilities, costs) to estimate the expected quality-adjusted life-years (QALYs) and costs associated with each treatment.

A limitation of Markov models is their assumption that transitions between states are independent of patient history or time spent within a state (i.e., “memoryless” property). This assumption can be overcome to some extent by using time-dependent probabilities based on survival analysis (Section B.3.3.3 Baseline CV event risk) and by adding health states (e.g., post-event states).

The model was developed in Microsoft Excel® and replicates a structure previously used in the context of NICE HTA submissions in similar cardiovascular conditions, including TA385 (160). This validated model structure was, in turn, based on the model presented in Ara *et al.* (2008) (161) and is frequently cited in the literature for interventions in CVD. A similar approach has also been used by Ward *et al.* (2007) (157), used to inform NICE CG181 (Statins for the prevention of cardiovascular events) (162), and by Cook et al. (2004) (163).

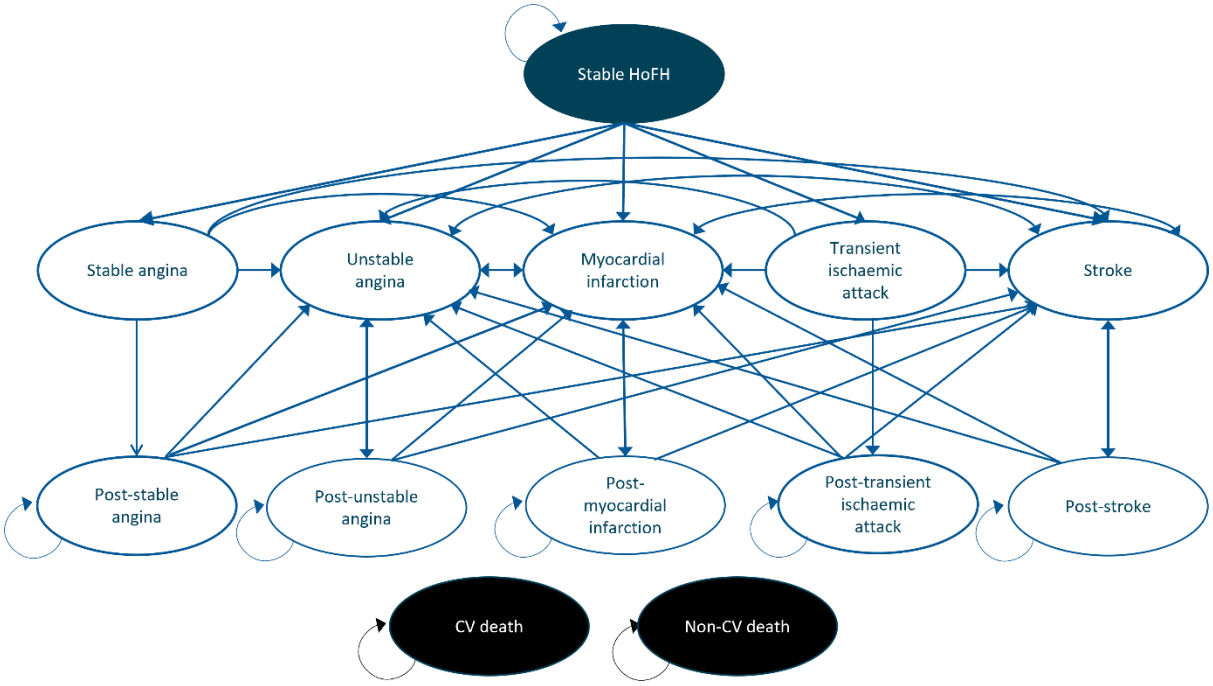
It is recognised that a limitation of applying these previous model structures and inputs in the current evaluation, is that these were applications in primary and secondary prevention of CVD in the general population. However, due to the rarity of HoFH, there is an absence of specific data sources available to validate and parameterise an alternative model structure.

At baseline, all patients are in the “stable HoFH” health state, in which patients are assumed to be CV-event naïve. From this state, patients can transition to five non-fatal primary CV event health states, based on the risk associated with each event, or to the dead state (due to CV causes or non-CV causes). The 5 primary non-fatal CV states are described as “stable angina” (SA), “unstable angina” (UA), “myocardial infarction” (MI), “transient ischaemic attack” (TIA) and “ischaemic stroke”. The health states included in the model are consistent with those used in previous NICE technology appraisals in relevant disease areas including NICE TA385 (160) and NICE TA694 (158). The model is represented schematically in **Error! Reference source not found.**. The description of each health state is provided in

Table 28 and the allowable transitions in the model are reported in

Table 30.

Figure 24. Schematic representation of cost-effectiveness model.



Abbreviations: CV, cardiovascular; HoFH, homozygous familial hypercholesterolemia.

Table 28. Description of health states in the model.

Health states	Definition
Stable angina	First occurrence of angina that only occurs during physical exertion
Post-stable angina	Patients whose stable angina began more than a year ago
Unstable angina	Occurrence of a form of acute coronary syndrome. An episode of angina that occurs randomly or unpredictably, including at rest
Post-unstable angina	Patients whose first episode of unstable angina was more than a year ago
MI	Non-fatal myocardial infarction. A form of acute coronary syndrome with permanent sequalae
Post-MI	Patients whose MI occurred more than a year ago
TIA	Transient ischaemic attack
Post-TIA	Patients whose TIA occurred more than a year ago
Stroke	Non-fatal ischaemic stroke
Post-stroke	Patients whose stroke occurred more than a year ago
CV death	Death due to any CV events
Non-CV death	Death due to any non-CV cause

To account for the increased impact on HRQoL and resource use of CV events in the first year, as well as the increased risk of experiencing a subsequent CV event, each non-fatal CV event is modelled in 2 stages. The first stage corresponds to an acute phase, accounting for cost and HRQoL impact in the first year following the event, and the second stage, described as a "post-event" health state, accounts for longer-term outcomes associated with each event. Patients in post-event health states can transit back to acute health states (signifying occurrence of another acute event). However, patients in any of the post-event health states cannot move back to stable angina or TIA health states. Patients can move to the dead state from any living health state, due to CV or non-CV related causes. Table 29 shows the transitions that are possible between acute and post-event health states.

In the model, patients can experience up to 1 event per annual cycle. In clinical practice, patients may experience multiple non-fatal CV events of different types, for instance, a patient may experience a stroke, followed by a MI. However, the model makes the simplifying assumption that the patient's healthcare resource use and HRQoL are determined by their most recent CV event. This is to avoid the complexity of modelling possible sequences of CV events, for which specific HRQoL or resource use data would likely not exist.

QALYs for the cohort are computed for each annual cycle by multiplying the proportion of the cohort in each state by the relevant age and gender adjusted utility multiplier for that state. Costs per cycle were summed using the same approach as was used for the QALYs.

Table 29. Allowed transitions between states.

Acute health states (From/To)	SA	UA	MI	TIA	Stroke	Post-SA	Post-UA	Post-MI	Post-TIA	Post-IS	CV Death
SA	×	✓	✓	×	✓	✓	×	×	×	×	✓
UA	×	×	✓	×	✓	×	✓	×	×	×	✓
MI	×	✓	×	×	✓	×	×	✓	×	×	✓
TIA	×	✓	✓	×	✓	×	×	×	✓	×	✓
IS	×	✓	✓	×	×	×	×	×	×	✓	✓
Post health states (From/To)	**SA**	**UA**	**MI**	**TIA**	**Stroke**	**Post-SA**	**Post-UA**	**Post-MI**	**Post-TIA**	**Post-IS**	**CV Death**
Post-SA	×	✓	✓	×	✓	✓	×	×	×	×	✓
Post-UA	×	✓	✓	×	✓	×	✓	×	×	×	✓
Post-MI	×	✓	✓	×	✓	×	×	✓	×	×	✓
Post-TIA	×	✓	✓	×	✓	×	×	×	✓	×	✓

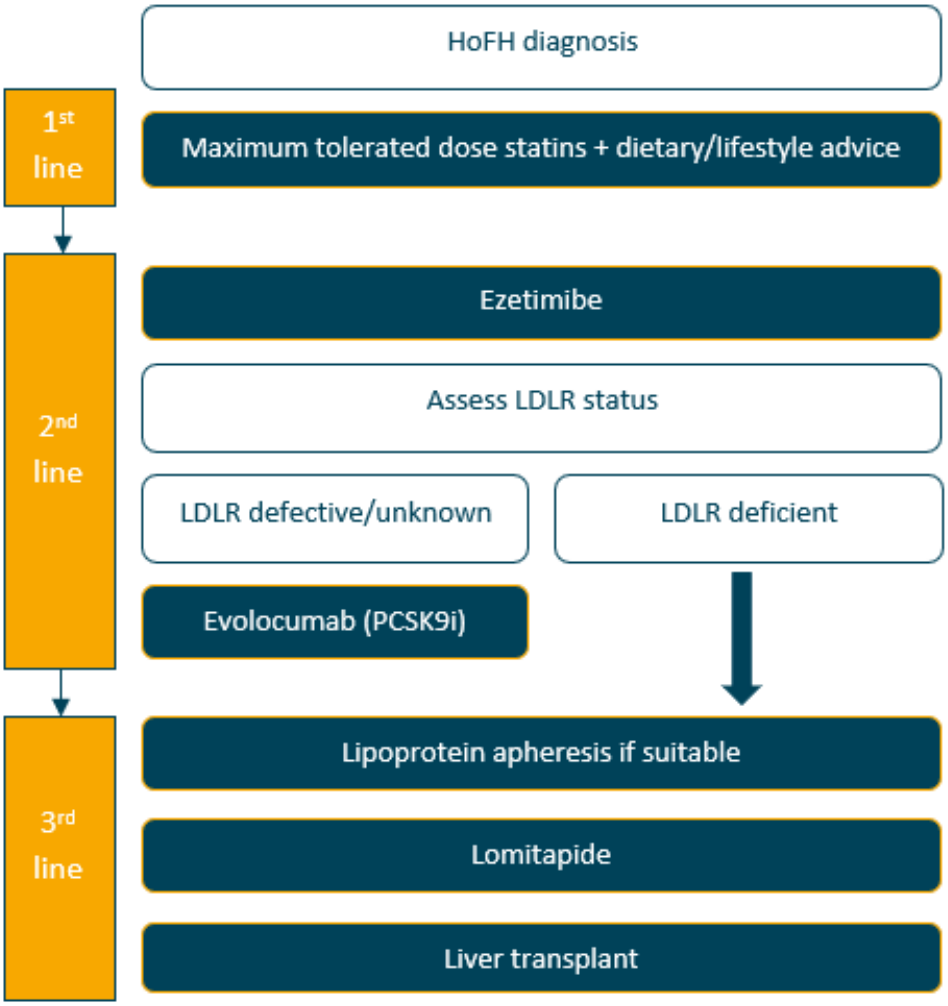
Post-IS	×	✓	✓	×	✓	×	×	×	×	✓	✓

Abbreviations: CV, cardiovascular; IS, ischaemic stroke; MI, myocardial infarction; TIA, transient ischaemic attack; SA, stable angina; UA, unstable angina.

B.3.2.5 Intervention and comparator

The objective of treatment in HoFH is to reduce LDL-C levels to target levels and thus reduce CVD risk. A summary of the current management algorithm of patients with HoFH in the UK is reported in Figure 25. More detailed information on the treatment pathway is reported in Section B.1.3.6 Patient management pathways. Individual treatment modalities are discussed in Section B.1.3.7 Pharmacological management and Section B.1.3.8 Non-pharmacological treatments.

Figure 25. Management pathway used in the model (comparator arm). Adapted from France *et al.* (2016) (20).



Abbreviations: HoFH, homozygous familial hypercholesterolemia; LDLR, low-density lipoprotein receptor; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

B.3.2.5.1 Intervention

The intervention in the economic model is evinacumab. Evinacumab has been implemented as an intervention in the cost-effectiveness model in line with its marketing authorisation.

The recommended dose for evinacumab is 15 mg/kg administered by intravenous (IV) infusion over 60 minutes once monthly (164). Thereafter, evinacumab can be scheduled monthly from the date of the last dose. It is expected that evinacumab will be administered either in a specialist outpatient setting or potentially in the future, by a district nurse at the patient's residence. The rate of infusion may be slowed, interrupted, or discontinued if the patient develops any signs of adverse reactions, including infusion-associated symptoms. Evinacumab can be administered to patients who receive LDL-apheresis (5).

The clinical effectiveness of evinacumab is fully discussed in Section B.2.6 Clinical effectiveness results of the relevant studiesB.2 Clinical effectiveness. The effectiveness values incorporated into the base case of the economic model are discussed in Section B.3.8.1 Summary of base-case analysis inputsB.3.6 Uncertainty, and values used in sensitivity analyses in Section B.3.10 Exploring uncertainty.

B.3.2.5.2 Comparator

The comparator treatment in the model is oral lomitapide. The principal evidence to support the efficacy of lomitapide was the single-armed pivotal trial by Cuchel *et al.* (2013) (87). This was considered more robust than the data reported in two retrospective registries (86, 165), which both had critical methodological limitations. The values used in the model, including a critique of these studies, is reported in Section B.3.2.5 Intervention and comparator, and values used in sensitivity analyses in B.3.10 Exploring uncertainty.

B.3.2.6 Long-term effectiveness

As HoFH is an incurable disorder, the base case in the model assumes a lifetime treatment duration if patients do not discontinue treatment due to AEs or other reasons. The treatment duration was applied in the same way for both the evinacumab and the lomitapide arm as different stopping rules could lead to errors in the interpretation of the results. It is assumed that as long as patients are on treatment, they will experience the full treatment effect on LDL-C level, corresponding to the treatment mix they are on. As there is a lack of high-quality long-term comparative efficacy data for evinacumab or lomitapide, it is assumed there was no reduction in treatment efficacy over the longer term. It was also assumed there would be no change in the unit costs of the drugs other than that reflected in the cost discounting, in line with NICE reference case (166).

B.3.2.7 Summary of model characteristics

A summary of the model characteristics is reported in

Table 30. Summary of model characteristics.

Table 30. Where applicable, all values were consistent with the NICE reference case (167).

Table 30. Summary of model characteristics.

Factor	Chosen values	Justification
Economic analysis	Cost-utility analysis expressed in terms of incremental cost per quality-adjusted life-year gained	In line with the requirements of HTA in the United Kingdom by NICE, and other efficiency based HTA agencies
Base case perspective	NHS and PSS	As per NICE reference case
Time horizon	Lifetime horizon (up to age of 100)	As stipulated by NICE reference case – long enough to capture differences in costs and outcomes associated with HoFH and modelled treatments
Cycle length	Annual	In line with previous NICE technology appraisals in similar CVD conditions
Half-cycle correction	Yes	As per NICE reference case
Treatment waning effect	No	No treatment waning effect will be assumed in the base case
Discount rate for utilities and costs	3.5%	As per NICE reference case
Source of utilities	Health state utilities: Targeted literature reviews in similar CVD conditions. Base case informed based on TA694 health state utilities Disutilities: associated with adverse events and treatment such as apheresis	Values were applied in previous NICE technology appraisals. See Section B.3.4 Measurement and valuation of health effects
Source of costs	Health state costs: Targeted literature review in similar CVD conditions. Base case informed based on TA694 health state costs Drug costs: British National Formulary (168)	Values were applied in previous NICE technology appraisals. See section B.3.5 Cost and healthcare resource use identification, measurement, and valuation

B.3.3 Clinical parameters and variables

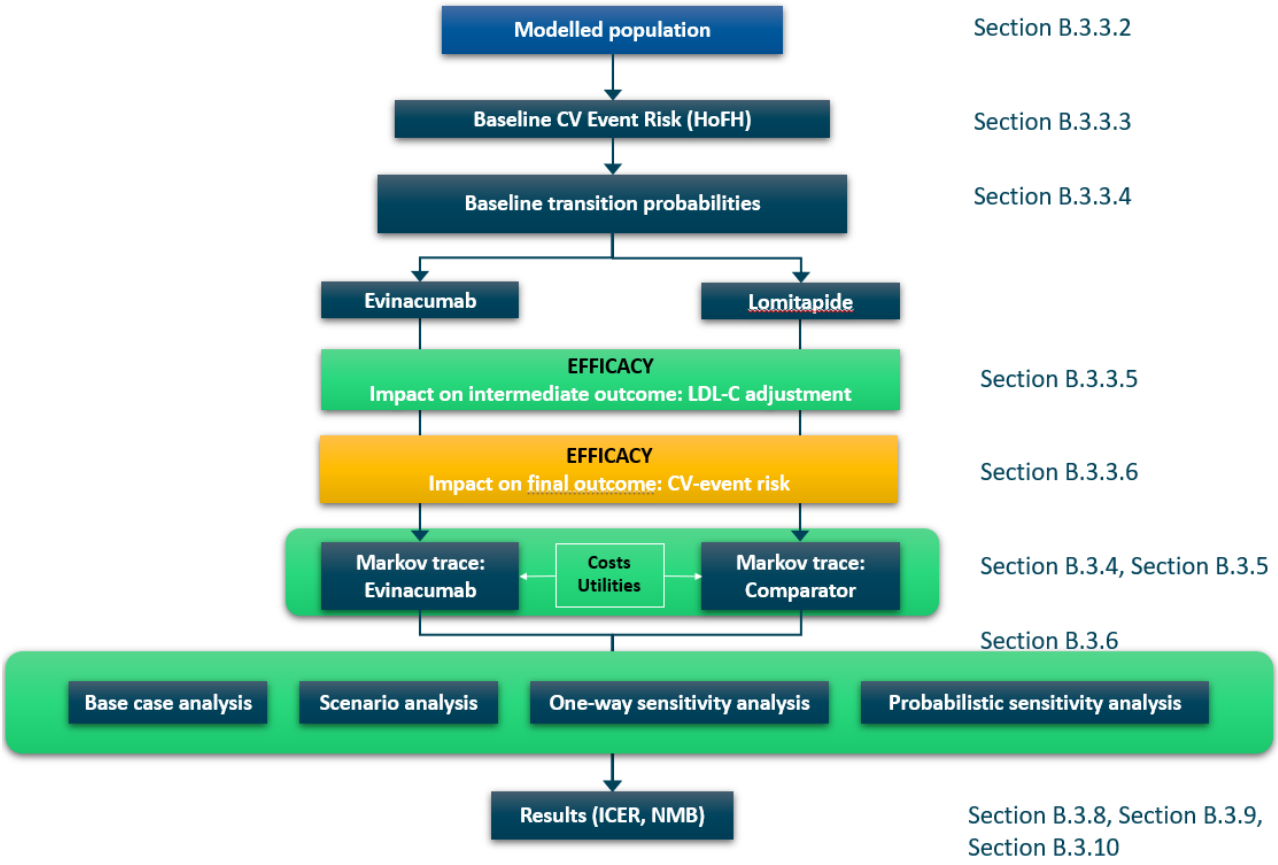
B.3.3.1 Overview of clinical inputs

The economic model estimates the effect of treatments in HoFH patients on the risk of CV events, along with the subsequent impacts on survival, HRQoL and costs. Since the pivotal study data for the intervention and comparator are not able to provide relative effect estimates on CV outcomes, the treatment efficacy is measured in terms of the intermediate outcome of circulating LDL-C concentration. Circulating LDL-C concentration is known to be causally related to the risk of CV events (Section B.1.3.2 Consequence of raised LDL-C).

The overall baseline risk of CV events was estimated from a HoFH specific study, whilst the distribution of CV events was informed by a study in the general population. The relationship between LDL-C reduction and CV events was based on a large meta-analysis of trials on statins. The efficacies for background treatments were based on individual trial data or data derived from an ITC. The efficacy of evinacumab and lomitapide, in the base-case, were derived from the ITC.

A summary of the methods used to determine the clinical effectiveness parameters used in the model is reported in Figure 26.

Figure 26. Flow chart summarising how inputs on clinical effectiveness are used.



Abbreviations: CV, cardiovascular; HoFH, homozygous familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NMB, net monetary benefit.

B.3.3.2 Baseline characteristics

B.3.3.2.1 Background treatment mix

The population modelled was largely based on that reported from the ELIPSE trial (5), in which recruited patients were receiving a range of LLTs positioned above evinacumab or lomitapide in the treatment pathway. A proportion of the cohort were receiving lomitapide, however, this is not included as a background treatment option since evinacumab is intended to displace lomitapide. It is assumed that the characteristics of the ELIPSE trial cohort, including background treatment mix, is representative of the target population for this evaluation. The background mix is reported in Table 32.

Table 31. Treatment mix used in the model.

Treatment	Use in model	Patients on treatment (%) – evinacumab arm	Patients on treatment (%) – comparator lomitapide arm
Atorvastatin	Background	93.8	93.8
Ezetimibe	Background	75.4	75.4
Evolocumab	Background	76.9	76.9
Apheresis	Background	33.8	33.8
Lomitapide	Comparator	0	100
Evinacumab	Intervention	100	0

For modelled patients, 32.3% were assumed to have null/null mutation (5), which renders statins and PCSK9 inhibitors ineffective. In the base case, it is assumed that the treatment effects of atorvastatin and evolocumab are not applied to HoFH patients with null/null mutations, and the treatment effects of apheresis, lomitapide and evinacumab are applied to the entire population cohort.

B.3.3.2.2 Baseline LDL-C level

The baseline LDL-C concentration for the target population was derived from the cohort reported in the study by Thompson *et al.* (2015) (156). This cohort is described below. This source was used, rather than the data from the ELIPSE study, since this corresponds to the baseline CV risk profile also derived from this source.

Thompson *et al.* (2015) reported patient level pre-treatment TC, HDL-C, TG and LDLC, as well as on-treatment TC. The post-treatment LDL-C concentration was estimated by assuming that the change in TC pre- and post-treatment is entirely due to the change in LDL-C. This provided an on-treatment LDL-C concentration for 27 subjects with complete data available across all measures.

A further 12 subjects provided pre- and post-treatment TC concentrations but were missing data for pre-treatment LDL-C concentration. A normal linear regression model was estimated using the complete data on pre-treatment TC and LDL-C concentration. This was then used to estimate the value of LDL-C for the 12 subjects with missing data. Post-treatment LDL-C for these subjects was derived based on the change in TC concentration as described above.

The mean on-treatment LDL-C concentration for 39 subjects obtained using data from Thompson *et al.* (2015) was 8.71 mmol/L. This study also reported the LLTs patients were receiving and compared with the ELIPSE trial population, considered most representative of current practice, the Thompson *et al.* (2015) cohort received a different mix of background treatments. It was, therefore, necessary to apply the treatment effects to account for differences in background treatments as well as to apply the effects of the intervention of comparator.

The proportions of patients receiving background LLTs in the ELIPSE study and Thompson *et al*. (2015) cohorts are presented in Table 33. By applying the efficacy in terms of relative change in LDL-C concentrations for these background treatments (Section B.3.3.2.1 Background treatment mix), to a proportion of patients, the LDL-C concentration estimated from Thompson *et al*. (2015) can be adjusted to reflect the treatment mix observed in the ELIPSE study cohort.

Applying the ELIPSE study treatment mix to the Thompson cohort (not including evinacumab or lomitapide), as described above, produces an estimated LDL-C concentration of 7.93 mmol/L. This can be compared with a baseline of 6.71 mmol/L reported in the ELIPSE trial (5), a 23% difference. However, this has not accounted for the 25% of patients receiving lomitapide in the ELIPSE study.

Table 32. Treatment mix used in the model.

Treatment	ELIPSE study cohort	Thompson *et al*. (2015)	Difference in treatment mix
Atorvastatin	93.8%	88.6%	5.2%
Ezetimibe	75.4%	70.5%	4.9%
Evolocumab	76.9%	0%	76.9%
Apheresis	33.8%	59.1%	-25.2%

B.3.3.3 Baseline CV event risk

B.3.3.3.1 Time to CV death

A targeted literature review was undertaken to identify the most appropriate study to inform the baseline CV event risk to use in the model. Following discussions with key opinion leaders (KoLs) in HoFH, the most appropriate source was identified as being the study by Thompson *et al.* (2015) (156). This was selected on the basis of the study being in an HoFH patient cohort and having been conducted in the UK. Additionally, the study reported individual patient data (IPD) allowing for the estimation of survival functions for outcome of time to CV death.

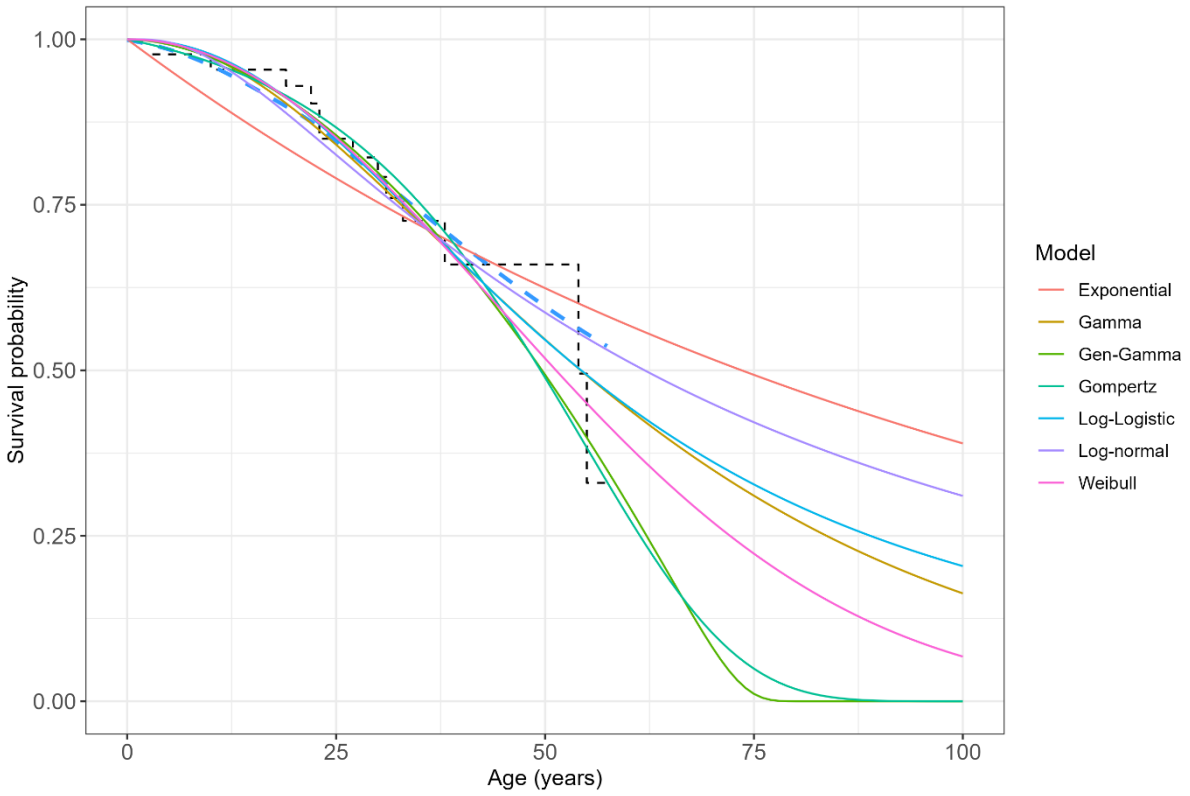
Thompson *et al.* (2015) (156) report a retrospective analysis of the demographic, clinical and genetic characteristics of the 44 homozygotes referred to Hammersmith Hospital over a 50-year period between 1964 and 2014. Patient-level data is available and includes LLTs received, CV outcomes, vital status, demographic features, lipid levels and genetic characteristics.

Among the Thompson *et al.* (2015) (156) patient population, 13 had died, 30 were alive, and 1 was lost to follow at the time of data collection. The mean pre-treatment TC concentration was 21.14 mmol/L and post-treatment TC concentration was 10.29 mmol/L. In this cohort, 89% of patients received statins, 59% received apheresis and 70.5% received ezetimibe. The IPD from Thompson *et al.* (2015) (156) is reported in Appendix D5. All deaths reported in the study were recorded as CV deaths.

Time to CV death from birth was modelled in a survival analysis that considered standard parametric models for the distribution of survival times. The use of spline models using 1 or 2 knots did not provide any significant improvements to the fit. Of the standard parametric models, the Gompertz model was considered the best-fit model and is used in the base-case. This was based on visual inspection of survival functions as well as comparison of the Akaike and Bayesian information criteria.

A plot of the Kaplan-Meier (KM) survival function (black dashed line), survival functions for all parametric models and a smoothed hazard estimate (blue dashed line) is shown in Figure 27. The KM curve and the fitted parametric models are reported in Appendix D5. In a scenario analysis the impact of using the distribution with the second-best fit (i.e., log-logistic) was explored (Section B.3.10 Exploring uncertainty). The survival analysis was performed using the R statistical programming software.

Figure 27. Derived survival curves for first CV event based on Thompson *et al.* (2015) and Ward *et al.* (2007).



Thompson *et al.* (2015) (169) was the preferred option for the base case analysis as it is more applicable to UK HTA context, in comparison to Raal *et al.* (2011) (170).

However, time to first non-fatal CV event or first major adverse cardiovascular event (MACE) was not reported for individual patients in this study.

Hence, a gender and age-adjusted ratio of non-fatal to fatal CV events over time was assumed to estimate the rate of non-fatal CV events over time, and subsequently the rate of first MACE over time.

B.3.3.3.2 Distribution of CV events

As described above, the time to first fatal CV event was modelled based on data from Thompson *et al.* (2015) (156). However, the time to first individual non-fatal CV events (e.g., non-fatal MI, non-fatal UA) were not reported in in this study. Hence, to inform the transitions between the health states of the cost-effectiveness model (Figure 24), additional evidence and assumptions were necessary to estimate the probabilities of specific CV events (e.g., MI, stable angina, ischaemic stroke).

Similar to previous NICE appraisals, TA385 (160) and TA694 (158), the gender and age specific distributions of CV events reported in Ward *et al.* (2007) (Table 33) Table 1were utilised to estimate the probabilities of individual non-fatal CV events. This distribution of CV events was based on the incidence of angina and MI data from the Bromley Coronary Heart

Disease Register and incidence of stroke and TIA data from the Oxfordshire Community Stroke Project (157), reflecting the distribution of CV events in the general population in the UK.

The data reported in Ward *et al*. (2007), shown in Table 33, were combined with the survival function for CV death (estimated using Thompson *et al.* (2015)) to obtain the probabilities of every fatal and non-fatal CV event. Firstly, the time varying hazard of non-fatal events was estimated by applying the ratio of non-fatal to fatal event incidence from Ward *et al.* (2007). This was then used to obtain the survival function for time to any CV event (fatal or non-fatal). The annual probability of any CV event that this function implies was then distributed across each event type using the proportions given in Table 33.

The proportions applied differ according to the age of the patient. Because the youngest age group reported in these studies was 40 to 54 years, it was assumed that the distributions for the 40 to 54 years age group are applicable to all younger age groups. This is a non-trivial assumption, but there are no equivalent data in people with HoFH or FH, who are affected by CVD at an earlier age than the general population and are at much higher risk. The appropriateness of using ratios for event rates from this general (high-risk) population study was not invalidated during discussions with clinical experts.

Table 33. Distribution of primary CV events as reported by Ward *et al.* (2015).

Gender	Age (years)	Stable angina	Unstable angina	MI	TIA	Stroke	CVD death	Total event rate per 1,000 persons per year
Male	40-54*	30.7%	10.7%	29.5%	6.0%	12.9%	10.1%	4.2
	55-65	32.8%	7.1%	17.2%	8.9%	20.6%	13.4%	13.7
	65-74	21.4%	8.3%	17.3%	10.0%	27.0%	16.0%	24.3
	75-84	19.1%	8.1%	16.1%	8.0%	34.3%	14.3%	37.5
	85-100	21.4%	9.6%	18.6%	1.6%	35.1%	13.7%	42.6
Female	40-54*	32.5%	11.7%	8.0%	16.0%	22.9%	9.1%	1.6
	55-65	34.6%	7.3%	9.2%	9.5%	28.8%	10.6%	6.6
	65-74	20.2%	5.2%	12.1%	7.3%	38.2%	17.1%	12.4
	75-84	14.9%	3.4%	10.2%	9.8%	46.4%	15.2%	23.4
	85-100	13.6%	2.9%	10.0%	8.7%	50.1%	14.7%	32.9

Abbreviations: CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack.

* An assumption will be made that the CV event distributions for the 45-54 age are applied to younger patient groups.

B.3.3.3.3 Alternate sources of baseline CVD risk

During the development of the model, other sources of baseline risk were considered for use in the base case or scenario analyses. Both were primary CVD risk assessment algorithms, namely the Framingham Risk Score (FHS) (171) and the QRISK3 algorithm (172).

The FHS is a predictive CVD risk algorithm used to estimate the 10-year probability of CVD events. It was developed based on a cohort of individuals from the general population (without a history of CVD) aged 30 to 74 years from Framingham, Massachusetts. However, the generalisability of this algorithm has been previously heavily criticised in TA394, as the derivation cohort was based on a single-centre study of otherwise healthy individuals, and did not reflect the high-risk population of that assessment (173). For this reason, this source of baseline CVD risk was discarded.

The QRISK tool was originally developed in 2007 (174). It is used to estimate a person's 10-year risk of developing a heart attack or stroke, based on UK general population aged 25 to 84 years without previous CVD events. The tool has undergone three iterations, with the latest version being QRISK3 (175). The QRISK tool has been previously recommended in NICE CG181 as the preferred method for risk scoring for primary prevention of CVD (162). The QRISK tool has also been used within the context of cost-effectiveness modelling in NICE, with TA385 using these source data (160).

A major limitation of applying QRISK3 to estimate CVD risk in HoFH is that this cohort of patients have very high levels of LDL-C, approximately 4 to 8 times higher compared with the general population (41). Therefore, as with the Framingham Risk Score and other similar predictive algorithms, it may not accurately predict CVD risk for HoFH patients, as in this context, HoFH patients could be statistical outliers. Additionally, CVD risk equations derived from non-FH populations are also likely to underestimate the CV risk patients with HoFH, due to the prolonged increase in LDL-C these patients experience, starting in childhood. The limitations and applicability of the QRISK3 tool has been identified in a previous NICE appraisal (160). Additionally, KOLs concurred that QRISK3 was not an appropriate source of data to estimate CVD risk in people with HoFH. For these reasons, its use was rejected, and instead HoFH specific data were applied, as reported in Thompson *et al.* (2015) (156).

B.3.3.4 LDL-C and risk of CV events

A common primary endpoint in CVD clinical trials is the proportional change in calculated LDL-C between baseline and follow-up, since most trials are not designed in terms of sample size and length of follow-up to directly evaluate the effect of treatments on CV event risk. In the absence of such data, the economic model has adjusted the baseline risks of CV events using evidence on the association between change in LDL-C concentration and CV event risks. This approach is consistent with previous cost-effectiveness models (158, 160).

In the base-case, the relationship between a unit reduction in LDL-C and the rate ratio for major CV events was sourced from a meta-analysis of the efficacy and safety of LDL-lowering therapy (23). Results of this meta-analysis are used, based on atherosclerotic CVD populations, since insufficient literature was available to formulate an equation specifically for an HoFH population (or indeed, populations with FH). This constitutes a limitation, particularly since the upper range values in HoFH typically exceed those observed in the general population (the normal range of LDL-C being 1.3 to 2.6 mmol/L).

This meta-analysis reported the rate ratio per 1 mmol/L change in LDL-C for various CV events (23). The results are presented in Table 34. Rate ratios for stable angina and TIA were assumed to be 1, as there is insufficient evidence to inform a relationship between the risk of these health states and a reduction in LDL-C. Within the economic model, the hazards for each type of event are adjusted based on a change in LDL-C according to Equation 1.

Equation 1. Relationship between CV event rate and LDL-C change.

$$r_{1,i} = r_{0,i}\left[\alpha_i^{(\mathrm{L}_0 - \mathrm{L}_1)}\right]$$

Where:
L_0 is the baseline LDL-C level in mmol/L
L_1 is the reduced LDL-C level in mmol/L
$r_{0,i}$ is the one-year rate for experiencing event i at the baseline LDL-C level of L_0
$r_{1,i}$ is the one-year rate for experiencing event i at the reduced LDL-C level of L_1
α_i is the rate ratio per unit reduction in LDL-C for event i

Following the application of this formula to adjust the hazards for each type of CV event, these were then converted into annual probabilities assuming constant hazards within each year. This approach was applied to the intervention and the comparator arm of the model separately, accounting for the total LDL-C reduction of the treatment mix in each arm, providing the model transition probabilities corresponding to the efficacy of each treatment option.

There are alternative sources for the relationship between change in LDL-C concentration and CV event risks that are available within the economic model. Navarese *et al.* (2015) compared PCK9 inhibitor treatment versus no PCK9 inhibitors in 10,159 adults with hypercholesterolaemia from 24 RCTs. Navarese *et al.* (2018), evaluated the association of LDL-C levels with total and CV mortality risk reductions, including a total of 34 trials in 268,288 patients, some of which received more intensive LDL-C lowering therapies (n=134,299) and some less intensive LDL-C lowering therapies (n=133,989). The rate ratios derived by these two studies and reported in TA694 are reported in Table 34.

Table 34. Rate ratio for CV events per 1mmol/L LDL-C reduction.

CV event	CTTC Meta analysis 2015 (23)	*TA694* *Navarese et al. (2015) (176)*	*TA694* *Navarese et al. (2018) (177)*
Stable angina	1	1	1
Unstable angina	0.76 (0.73-0.79)	0.64 (0.43-0.96)	0.85 (0.78-0.96)
MI	0.76 (0.73-0.79)	0.64 (0.43-0.96)	0.85 (0.78-0.96)
TIA	1	1	1
Stroke	0.85 (0.80-0.89)	0.64 (0.43-0.96)	0.99 (0.86-1.08)
CV death	0.88 (0.84-0.91)	0.64 (0.43-0.96)	0.89 (0.73-1.01)

Abbreviations: CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TIA, transient ischaemic attack.

B.3.3.4.1 Increased risk of subsequent cardiovascular events

Patients with a prior CV event are expected to have a higher risk of future CV events, compared with CV event naïve patients. NICE TA694 for bempedoic acid (158) and TA393 for alirocumab (178) have applied a relative risk increase of 1.5 estimated by Smolina *et al.* (2012) (179) to reflect the increased probability of CV death in all post-event health states. These authors estimated that, based on a sample of 387,000 MIs in England, the risk of death in survivors of MI was 1.5 times higher than that for survivors of a first MI.

In line with NICE TA694 and TA393 (158, 178), this economic model applies a 1.5 fold increase in the baseline hazards of CV death in all post-event health states. The same increase was applied to the risk of non-fatal cardiac events (SA, UA, MI) due to previous non-fatal cardiac events, and to the risk of non-fatal cerebrovascular events (TIA, IS) due to previous non-fatal cerebrovascular events.

As per NICE Evidence Review Group (ERG) comment in TA694, a relative risk of 1.2 was applied to recurrent cardiac events due to previous non-fatal cerebrovascular events and to recurrent cerebrovascular events due to previous non-fatal cardiac events.

To prevent the estimated probabilities of subsequent individual CV events from being over 1, the relative risks ratios presented in

Table 35 were applied to the hazards for each event.

Table 35. Relative risks used to capture the increased probability of multiple CV events.

Increase in probability of recurrent event	Relative risk (mean)
Risk ratio in cardiac events (SA, UA, MI) due to previous cardiac event (SA, UA, MI)	1.5
Risk ratio in cardiac events (SA, UA, MI) due to cerebrovascular event (Stroke, TIA)	1.2
Risk ratio in cerebrovascular events (Stroke, TIA) due to previous cardiac event (SA, UA, MI)	1.2
Risk ratio for cerebrovascular events (TIA, stroke) due to previous cerebrovascular events (TIA, stroke)	1.5
Risk ratio of CV death due to history of prior event	1.5
Abbreviations: CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack.	

B.3.3.4.2 Non-CVD death

The model must also account for mortality due to non-CV related causes. This was approximated by the general population all-cause mortality, assuming the impact of double counting due to CV related deaths in the general population to be negligible. For the UK population, all-cause mortality was derived from the UK life tables published by the Office for National Statistics (180). This was used to estimate the annual probability of death from non-CV related causes for each year of age, weighted according to the proportions of patients of each sex in the ELIPSE clinical trial.

B.3.3.5 Treatment efficacy

All the treatments for HoFH featured in the model (background treatment, intervention, and comparator) elicit their effect through reducing levels of circulating LDL-C, thereby reducing the risk of CV events, as described in Section B.3.3.3.3 Alternate sources of baseline CVD risk

During the development of the model, other sources of baseline risk were considered for use in the base case or scenario analyses. Both were primary CVD risk assessment algorithms, namely the Framingham Risk Score (FHS) (171) and the QRISK3 algorithm (172).

The FHS is a predictive CVD risk algorithm used to estimate the 10-year probability of CVD events. It was developed based on a cohort of individuals from the general population (without a history of CVD) aged 30 to 74 years from Framingham, Massachusetts. However,

the generalisability of this algorithm has been previously heavily criticised in TA394, as the derivation cohort was based on a single-centre study of otherwise healthy individuals, and did not reflect the high-risk population of that assessment (173). For this reason, this source of baseline CVD risk was discarded.

The QRISK tool was originally developed in 2007 (174). It is used to estimate a person's 10-year risk of developing a heart attack or stroke, based on UK general population aged 25 to 84 years without previous CVD events. The tool has undergone three iterations, with the latest version being QRISK3 (175). The QRISK tool has been previously recommended in NICE CG181 as the preferred method for risk scoring for primary prevention of CVD (162). The QRISK tool has also been used within the context of cost-effectiveness modelling in NICE, with TA385 using these source data (160).

A major limitation of applying QRISK3 to estimate CVD risk in HoFH is that this cohort of patients have very high levels of LDL-C, approximately 4 to 8 times higher compared with the general population (41). Therefore, as with the Framingham Risk Score and other similar predictive algorithms, it may not accurately predict CVD risk for HoFH patients, as in this context, HoFH patients could be statistical outliers. Additionally, CVD risk equations derived from non-FH populations are also likely to underestimate the CV risk patients with HoFH, due to the prolonged increase in LDL-C these patients experience, starting in childhood. The limitations and applicability of the QRISK3 tool has been identified in a previous NICE appraisal (160). Additionally, KOLs concurred that QRISK3 was not an appropriate source of data to estimate CVD risk in people with HoFH. For these reasons, its use was rejected, and instead HoFH specific data were applied, as reported in Thompson *et al.* (2015) (156).

B.3.3.4. The efficacy of LLTs was reported as the reduction in LDL-C, expressed as a percentage change relative to either baseline or a comparator arm (i.e., placebo). The economic model uses these relative effects to modify the baseline LDL-C concentration, which subsequently changes the patients' risk of experiencing CV events.

B.3.3.5.1 Indirect treatment comparison

Results from the evinacumab clinical trial ELIPSE show significant improvements in LDL-C, reporting a reduction of 49% from baseline compared with placebo in HoFH patients treated for 24 weeks (5); however, due to the rarity of HoFH, the efficacy of evinacumab and lomitapide (or other treatment comparators) were not directly compared within the ELIPSE study. Therefore, an ITC study was conducted to estimate the relative efficacy of evinacumab compared with other treatments among adult patients with HoFH aged 12 years or older (181). The clinical effectiveness of evinacumab is described fully in Section B.2.6 Clinical effectiveness results of the relevant studies and the ITC is described in B.2.9 Indirect and mixed treatment comparisons.

In the ITC study, an SLR was conducted to identify relevant clinical trials and RWE in HoFH patients. Following the stage of full text screening, four studies were identified and included in the ITC including:

- ELIPSE trial for evinacumab (5) (intervention)
- Cuchel *et al.* (2013) (87) for lomitapide (comparator)
- Gagne *et al*. (2002) (75) for ezetimibe (background treatment)
- Raal *et al.* (2015) (5) for evolocumab (background treatment)

Adjustments were made to utilise patient-level data from the ELIPSE trial and published aggregate data from the included lomitapide, ezetimibe and evolocumab trials. Matching-adjusted indirect comparisons were conducted for comparing evinacumab to lomitapide and ezetimibe, as these trials did not share a common comparator to conduct an anchored comparison. Matching was conducted based on potential prognostic factors and treatment effect modifiers; namely age, coronary heart disease status and baseline LDL-C.

For the comparison between evinacumab and evolocumab, a common comparator was available, and a Bucher ITC was used due to the availability of a control arm in both studies. In the ELIPSE trial, about half of the participants who received a PCSK9 inhibitor actually received alirocumab, however, for the purposes of the model these patients were assumed to have received evolocumab. The efficacy of evolocumab and alirocumab in HoFH are similar (78, 84).

Efficacy data for atorvastatin was taken from a multicentre 8-week open-label study in 89 HoFH patients (106). A mean reduction of 20% in LDL-C was achieved for these patients. This value was assumed for all high-intensity statins which are used for the treatment of HoFH.

The efficacy for LDL apheresis in HoFH is variable and dependent on factors such as the technology, the frequency of the procedure and the method of calculation. A central estimate of 37.1% was used, taken from a study of a cohort of patients receiving LDL apheresis in France (165). This study was selected because it was relatively large (n=29), it reported a

procedural frequency consistent with UK clinical practice (once every 2 weeks in most patients), and it was explicit in how the efficacy value was derived (calculation based on the interval mean). The estimates of LDL efficacy from this was consistent with values reported in literature reviews, where it has been reported the technology delivers change in LDL-C of between -40% and -30% (95, 96).

Results of the ITC were used in the model to inform the efficacy of evinacumab, lomitapide, evolocumab, and ezetimibe. Table 36 summarises the percentage change in LCL-C for evinacumab and comparators as reported in the ITC.

Table 36. Efficacy of interventions used in the model.

Treatment	LDL-C efficacy	Source
Atorvastatin	-20.0%	SPC (182), clinical trial (106).
Ezetimibe (10 mg)	-20.7%	MAIC (181). Same value as RCT from Gagne *et al.* (2002) (75).
Evolocumab (420 mg monthly)	-30.8%	Bucher's ITC (181). Original data from TESLA B (78).
Lomitapide	-40.1%	MAIC (181). Same value as ITT data from Cuchel *et al.* (2013) (87).
LDL apheresis	-30.7%	Retrospective cohort study (165).
Evinacumab	-55.1%	MAIC (181). Original data from ELIPSE (5).

Abbreviations: ITC, indirect treatment comparison; LDL-C; low-density lipoprotein cholesterol; MAIC, match adjusted indirect comparison; SPC, summary of product characteristics

B.3.3.5.2 Application of treatment effects

The efficacies of LLTs provided in Table 36 were combined with the change in the proportions of background treatments received (Table 32), to calculate the patients' LDL-C concentration after receiving the mix of treatments observed in the ELPISE pivotal study, excluding evinacumab and lomitapide. The change in the mix of background treatments is based on the comparison to the treatments received by the cohort reported in the Thompson *et al*. (2015) study (described earlier in Section B.3.3.2 Baseline characteristics and used to model baseline CV risks). This requires applying the treatment effects to an additional fraction of the cohort receiving a treatment (e.g., ezetimibe), or removing the effect from a fraction of the cohort not receiving a treatment (e.g., apheresis). Finally, the efficacies for the intervention or comparator are applied to obtain the final LDL-C concentration for each option which is then used to calculate the fall in LDL-C.

This approach has assumed that treatment effects are independent of other treatments received. As has been discussed, in practice multiple treatments are required in HoFH to

achieve target LDL-C levels, and this is reflected in the model by the application of constant relative efficacies, with no synergy or antagonism being modelled. This is justified because all the treatments included in the model have different mechanisms of action, with no known interactions with each other. In the case of evinacumab, it has been observed in the ELIPSE trial that its efficacy is consistent regardless of concomitant use of LLT, including apheresis (5).

B.3.3.6 Adverse events

Adverse events were not included in the economic models submitted to NICE in TA385 (160), TA393 (178) or TA694 (158) as no relevant economic or utility differences in the safety profiles of the drugs in the model (statins, ezetimibe, and evolocumab) were identified. Most of the major AEs reported in clinical studies of treatments in HoFH are CV mediated AEs, and thus it is often not possible to separate causal AEs from lack of efficacy. Clinical studies of evinacumab have reported a good safety profile (5).

Lomitapide is associated with frequent AEs including nausea, vomiting, diarrhoea. However, as these AEs were not graded, for instance using the Common Terminology Criteria for Adverse Events (CTCAE) criteria (183), their impact could not be modelled and they were not included. The non-inclusion of the cost and HRQoL impact of AEs associated with lomitapide is an assumption that is expected to be biased in favour of lomitapide.

For apheresis, a meta-analysis revealed a general consensus across reviewed studies that LDL apheresis is well-tolerated, and serious AEs occur very rarely (96). Therefore, the impact of AEs on utilities and costs were not captured in the model base case. Additionally, as lomitapide has known hepatoxicity, which could potentially be serious, costs associated with monitoring were included (Section B.3.5.4 Cost of monitoring).

B.3.3.7 Treatment discontinuation

For evinacumab, none of the 65 patients enrolled in the pivotal study discontinued due to adverse events during the study period (87). Therefore, the economic model conservatively assumes 100% treatment persistence on evinacumab. Furthermore, the potential for discontinuation of any background treatment (e.g., statins) is not considered. Since the intervention and comparator treatment efficacy is based on the ITT population, no adjustment to efficacy is required to account for discontinuation. Data from the ITT population was required for matching purposes for the lomitapide efficacy data derived from the ITC.

Following discontinuation due to adverse events, assumed to occur within 26-weeks of treatment initiation, there is potential for longer term attrition in both the lomitapide and evinacumab arms. Due to an absence of any evidence to inform estimates of the relative long-term treatment persistence for these treatments, the model base-case assumes no patients discontinue either treatment beyond week 26, thus the effect of discontinuation on efficacy was not double counted. This one-off discontinuation is applied to the intervention and comparator treatments only (i.e., does not apply to background treatment). If the

selected comparator (e.g., lomitapide) was already included in the background treatment mix of the study informing baseline CV event rates, then discontinuation probability is not applied to the percentage of patients who were already on this treatment. For instance, if 20% were on lomitapide in the study informing the baseline CV event-rates (i.e., Thompson 2015) and lomitapide is selected as the comparator, then discontinuation rates are applied to only to the additional 80% of patients.

B.3.3.7.1 Pharmacological treatments

In the pivotal study of lomitapide, a proportion of subjects discontinued due to adverse events. Over the 26-week efficacy phase, out of 29 subjects that were enrolled, 4 discontinued due to adverse events (87). This was implemented within the economic model as 13.79% of the cohort discontinuing at Week 26, leading to a reduction in the overall cost in the comparator arm.

For evinacumab, none of the 65 patients enrolled in the pivotal study discontinued due to adverse events during the study period (5) (Appendix D3.1). Therefore, the economic model assumes 100% treatment persistence on evinacumab. This assumption is expected to be biased against evinacumab in terms of cost-effectiveness. Furthermore, the potential for discontinuation of any background treatment (e.g., statins) is not considered.

Since the intervention and comparator treatment efficacy is based on the ITT population, no adjustment to efficacy is required to account for discontinuation. Data from the ITT population was required for matching purposes for the lomitapide efficacy data derived from the ITC.

Following discontinuation due to adverse events, assumed to occur within 26-weeks of treatment initiation, there is potential for longer term attrition in both the lomitapide and evinacumab arms. Due to an absence of any evidence to inform estimates of the relative long-term treatment persistence for these treatments, the model base-case assumes no patients discontinue either treatment beyond Week 26 (Section B.3.3.6 Adverse events).

Discontinuation of other pharmacological treatments (background therapy) were assumed to be 0% in the short and longer-term. Discontinuation data used in the base case of the model is reported in Table 37.

Table 37. Discontinuation rates applied in the model base case.

Treatment	Probability of discontinuation (26-weeks)	Annual probability of discontinuation after 26-weeks
Atorvastatin	0.00%	0.00%
Ezetimibe	0.00%	0.00%
Evolocumab	0.00%	0.00%
Lomitapide	13.79%	0.00%
Apheresis	0.00%	0.00%
Evinacumab	0.00%	0.00%

B.3.3.7.2 LDL apheresis discontinuation

Effective pharmacological treatment for HoFH may reduce the need for LDL-apheresis in some individuals. In the lomitapide open label single-arm study conducted by Cuchel *et al.* (2013) (87), 8 patients achieved LDL-C levels <2.6 mmol/L at Week 26. Based on the LDL-C response, 3 participants permanently discontinued LDL apheresis and 3 subjects permanently increased the time interval between apheresis treatments at some point during Weeks 26 to 78. Hence, in the cost-effectiveness model, it was assumed that 10.3% (i.e., 3 out of 29 patients in the ITT cohort) of patients on lomitapide discontinue apheresis due to well controlled LDL-C levels.

According to the ITC, evinacumab efficacy is expected to be higher than lomitapide. Hence, a conservative assumption was made in the model that evinacumab is expected to lead to an equivalent reduction in apheresis use. It was assumed that no other treatments would result in a reduction of apheresis use.

Based on expert opinion, it was assumed that LDL-C levels in patients who discontinue apheresis would increase after discontinuing apheresis. In the absence of further evidence, it has been assumed that the LDL-C concentration in patients who discontinue apheresis returns to the levels observed in those who have not undergone apheresis. Therefore, a reduction in apheresis results in a lower treatment cost and an increase in patients' LDL-C levels.

B.3.4 Measurement and valuation of health effects

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

Utility values were obtained from EQ-5D data collected in the ELIPSE trial. Values were not used in the model but are reported in Section B.2.6.2 Secondary outcomes

B.3.4.2 Mapping

No mapping of utilities was used in this model.

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

An SLR was undertaken to identify HRQoL studies relevant to the decision problem, described in Appendix H. Two studies were identified. Kayikcioglu *et al*. (2019) reported HRQoL results from the AHIT-1 registry (46). These were derived from uncontrolled observational data using the Short Form 36 (SF-36) tool and were not appropriate for use in the model. Mulder *et al*. (2022) reported that EQ-5D scores were lower in people with HoFH compared with the general Dutch population (184). However, these data were not useable in the model.

B.3.4.4 Adverse reactions and treatment-related disutility

As detailed in Section B.2.10.5 Adverse events of special interest, in line with previous appraisals of ezetimibe, alirocumab and bempedoic acid, the impact of treatment-related adverse events has not been accounted for in the model.

Lomitapide is associated with frequent GI-related AEs, such as diarrhoea, nausea, vomiting and abdominal pain, but most of them are mild to moderate in intensity. All other treatments have a good safety profile. In the model base-case, these frequencies are set to zero for all treatments.

LDL apheresis has been associated with lowered HRQoL in patients with HoFH (46). Data on apheresis-related disutility was not available in the literature, therefore, treatment-disutility of haemodialysis was used as a proxy for apheresis. Haemodialysis is provided on average 3 times a week for 3-5 hours (assuming 4 as the average) and has a disutility value of -0.164 (185). Apheresis is provided in the model once every two weeks and is carried out for 2 to 3 hours (assuming 2.5 hours as the average).

For the estimation of apheresis disutility, it was assumed that haemodialysis and apheresis disutility per hour is equivalent. Therefore, the annual utility decrement for apheresis was calculated by applying the disutility of haemodialysis for the duration and frequency of apheresis. Therefore, in the model base case, LDL apheresis was associated with a disutility value of 0.0171.

All other treatments were assumed to have no treatment-related impact on utility.

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

Hypercholesterolaemia is considered an asymptomatic condition, hence its impact on patient's HRQoL can be indirectly captured through the increased risk of CV events associated with the condition. However, no studies reporting utility values in HoFH patients for the modelled health states were identified in the SLR. A targeted search to identify utility values for the modelled health states in other cardiovascular conditions was conducted. Priority was given to utility values based on the EQ-5D quality of life measure using the UK value set and used in previous NICE TAs of CVD treatments.

Health state utilities used in the model, along with the corresponding mean age and the justification for their use are described in Table 38.**Error! Reference source not found.** An alternative set of utility values for the modelled health states that are used for scenario analysis are presented in

Table 42. The health state utilities reported in Table 38 correspond to patients with a specific mean year of age. The utility for each health state that is applied in each model cycle as the cohort ages is, therefore, adjusted to account for the impact of aging on quality of life. This has used a formula, characterising the trend in health state utilities for the UK general population (186), given in **Error! Reference source not found.**.

Equation 2. UK EQ-5D utilities based on age and gender.

$$\text{EQ-5D utility} = 0.9454933 + 0.0256466 \times \text{male} - 0.0002213 \times \text{age} - 0.0000294 \times \text{age}^2$$

The formula in Equation 2 is used to calculate an adjustment factor for each model cycle and health state that is then applied to the reference utility for each health state. The adjustment factor is calculated as the ratio of the predicted general population utility, at the age of the cohort in each cycle, to the predicted general population utility at the reference age of the cohort from which the health state utility was obtained. The proportion of the cohort that are male, required in Equation 2, was based on the ELIPSE study cohort characteristics.

As an example, to estimate the utility adjustment factor for MI, we first used the 0.615 utility value for MI that corresponds to patients who are on average 69 years old (Table 41). Then using the formula above, we estimated that the general population utility for patients of the same age (and 46% male as in ELIPSE study) is 0.802. Finally, we calculated the multiplier for MI as 0.767 (0.615/0.802). Then the utility in each model cycle for patients who were in the MI health state was estimated by applying this adjustment factor to the general population's age specific utility value. The same approach was followed for all health states.

Health state utility values used in a previous NICE appraisal of ezetimibe (TA385) were selected for a scenario analysis to assess the impact of health state utility on results. The same age adjustment described above for the base case was applied to obtain age-adjusted utility values.

Table 42 presents the alternative source for utility values used in the scenario analysis.

Table 38. Health-state utility values used in the model.

Health state	Utility values	Corresponding age	Source	Justification
Stable angina	0.615	69	Ara and Brazier (2010) (186)	Used in TA694
Post-stable angina	0.775	68	Ara and Brazier (2010) (186)	Used in TA694
Unstable angina	0.615	69	Ara and Brazier (2010) (186)	Used in TA694
Post-unstable angina	0.775	62	Ara and Brazier (2010) (186)	Used in TA694
MI	0.615	69	Ara and Brazier (2010) (186)	Used in TA694
Post-MI	0.742	65	Ara and Brazier (2010) (186)	Used in TA694
Stroke	0.625	68	Ara and Brazier (2010) (186)	Used in TA694
Post-stroke	0.668	67	Ara and Brazier (2010) (186)	Used in TA694
TIA	0.760	73	Luengo-Fernandez *et al*. (2013) (187)	Only publication that is consistent with NICE reference case; used in CG181 and TA385
Post-TIA	0.760	73	Luengo-Fernandez *et al*. (2013) (187)	Only publication that is consistent with NICE reference case; used in CG181 and TA385

Abbreviations: MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; TIA, transient ischaemic attack.

Table 39. Alternative source for utility values.

Health state	Utility values	Corresponding age	Source	Justification
Stable angina	0.808	68	Melsop *et al.* (2003)	Used in CG181 and TA385

Post-stable angina	0.808	68	Melsop *et al.* (2003)	Used in CG181 and TA385
Unstable angina	0.770	49	Goodacre *et al.* (2004)	Only published data consistent with NICE reference case; consistent with TA385 and CG181
Post-unstable angina	0.800	62	Ara *et al*. (2008)	Evidence of small increase in HRQoL over time; consistent with TA385
MI	0.760	49	Goodacre *et al*. (2004)	Consistent with NICE reference case and used in previous appraisals
Post-MI	0.800	62	Lacey and Walters 2003	Evidence of HRQoL improves over time; consistent with TA385
Stroke	0.500	70†	Tengs and Lin (2003), weighted by severity from Youman *et al.* (2003)	Evidence of low HRQoL in the first 6-month post event; meta-analysis; consistent with CG181 and TA385
Post-stroke	0.628	70†	Tengs and Lin (2003), weighted by severity from Youman *et al.* (2003)	Meta-analysis
TIA	0.760	73	Luengo-Fernandez *et al.* (2013)	Only publication that is consistent with NICE reference case; used in CG181 and TA 385
Post-TIA	0.760	73	Luengo-Fernandez *et al.* (2013)	Only publication that is consistent with NICE reference case; used in CG181 and TA 385

Abbreviations: MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; TIA, transient ischaemic attack.

†Mean age used for stroke and post-stroke is taken from Duncan et al 2000, a study included in Tengs and Lin (2003). The study was chosen as it had the largest sample size and weight among all studies included in Tengs and Lin (2003).

B.3.5 Cost and healthcare resource use identification, measurement, and valuation

A systematic literature review was conducted to identify costs and healthcare resource use associated with management of HoFH and its complications (Appendix I). No utilisable data were identified.

The perspective of the base case is that of the UK NHS and PSS. All costs in the model were expressed in GBP (£). The CEM includes the following costs:

- Drug acquisition costs
- Administration costs
- Monitoring cost
- Health state costs
- Adverse event costs

All costs were inflated to 2020 price level using the cost inflators provided in the Unit Costs of Health and Social Care 2021 report (188).

B.3.5.1 Drug acquisition costs

Drug acquisition costs were estimated by combining information on drug utilisation and unit costs for both the evinacumab and the comparator arm. Drug utilisation was estimated based on the recommended drug dosages for each treatment.

Drug acquisition costs were sourced from the most recent British National Formulary (BNF) (168). Treatment costs, corresponding to the model's cycle length, were estimated based on the dosage for HoFH patients, reported in Table 40. Drug costs were applied to each modelled arm based on the percentage of patients who are on each drug. The drug costs for each arm in the model were adjusted to reflect discontinuation of treatments that lead to a change in the treatment mix within each modelled arm.

A PAS discount of [redacted](agreed by NHSE), is applied on the evinacumab list price, which is used in the base case. The price, based on the discount, is [redacted]

Table 40. Treatment costs used in the model.

Treatment	Administration method	Unit	Unit price	Dose	Annual cost	Source
Background treatment (apply to both intervention and comparator arms)						
Atorvastatin 80 mg	Oral	28 tablets	£1.42	80 mg once daily	£18.52	NICE BNF 2022
Evolocumab 140 mg per 1ml	Self-injection	2 pre-filled disposable injections	£340.2	420 mg monthly	£6,656.68	NICE BNF 2022

Ezetimibe 10 mg	Oral	28 tablets	£1.67	10 mg once daily	£21.78	NICE BNF 2022
LDL apheresis	IV access	1 session	£1,526.25	1 session every 2 weeks	£39,818.94	Thompson *et al.* (2008)
Comparator						
Lomitapide (5 mg/10 mg/20 mg)	**Oral**	**28 capsules**	**£17,765 (prices are the same for all strengths)**	**10-60 mg daily**	**£513,854.00**	**NICE BNF 2022**
Intervention						
Evinacumab 345 mg	**IV**	**1 vial**	[redacted]	**15 mg/kg body weight monthly**	[redacted]	**Company data**

Unit costs and dosage per administration associated with each treatment are presented in Table 40. Treatment costs used in the model. Atorvastatin was assumed to be administered at 80 mg once daily and ezetimibe at 10 mg once daily. Evolocumab was assumed to be administered at 420 mg monthly, requiring 3 pre-filled disposable injection pens per administration.

In the base-case, lipoprotein apheresis is assumed to be administered once every 2 weeks. The cost of lipoprotein apheresis was sourced from Thompson *et al.* (2008) (189) and inflated to 2020 price level. An alternative cost and frequency of apheresis were assessed in the scenario analysis (Section B.3.10 Exploring uncertainty).

B.3.5.2 Cost of treatment (evinacumab)

Evinacumab is administered as an infusion (drip) into the vein for 60 minutes every month, at a recommended dose of 15 mg/kg.

For the evinacumab arm, it was assumed in the base case that patients could receive only whole vials, and therefore accounting for drug wastage due to vial size. To estimate the number of evinacumab vials per treatment administration, the indicated dosage (15 mg/kg) and content per vial (345 mg) were used to calculate weight thresholds that determine the number of vials required by patients. Based on the content per vial and the indicated dosage, weight thresholds corresponding to different number of vials were calculated. To estimate the proportion of patients between each threshold weight, hence the proportion of patients requiring a specific number of vials, it was assumed that patients' weight follows a lognormal distribution with a mean weight of 72.7 kg (log of mean weight = 4.25) and a standard deviation of 20.53 kg (standard deviation of log mean weight = 0.26) as reported in

the ELIPSE study (5). The full wastage rate of evinacumab for patients with this specific weight distribution was estimated to be 14.5%. These data are reported in Table 41.

Table 41. Number of evinacumab vials required for different weight (kg).

Number of vials	Weight threshold	Proportion (based on lognormal distribution)
6 small vials	138	3.6%
5 small vials	115	12.5%
4 small vials	92	35.9%
3 small vials	69	41.5%
2 small vials	46	6.5%
1 small vial	23	0.0%
Weighted average: 3.7 vials Full wastage rate = (3.7*345-15*72.7) / (3.7*345) * 100% = 14.5%		

A scenario analysis was conducted to allow vial sharing. For the vial sharing scenario, the cost per mg of evinacumab was applied to the average weight of patients in the ELIPSE study. The annual cost of evinacumab is [redacted] when vial sharing is permitted.

Costs associated with treatment administration were also included in the model. It was assumed that none of the background and comparator treatments were associated with an administration cost as they are administered orally or by self-injection.

Evinacumab is administered as an infusion (drip) into the vein for 60 minutes every month, thus an administration cost (188) was applied to the evinacumab arm, for as long as patients were on treatment. In the base case, it was assumed that 1 hour of nursing time per month in an outpatient setting is required, corresponding to an annual administration cost of £504.

B.3.5.3 Cost of treatment (lomitapide)

The dose of lomitapide in the base case was estimated based on data from the pivotal phase 3 trial (87) (Table 42). Weighted by the proportion of patients receiving corresponding does, the average number of capsules per day was 2.22. This value was used because it is intrinsically linked to the efficacy data used in the model. It is worth noting that, calculations regarding lomitapide dosing were based on the fact that the maximum strength of lomitapide is 20mg per capsule in the UK.

Table 42. Dosage of lomitapide used in the base case (from Cuchel *et al* (2013)).

Lomitapide dose/daily	Proportion of patients
1 capsule	26%
2 capsules	26%
3 capsules	48%

As lomitapide is taken orally, no additional administration costs were included.

B.3.5.4 Cost of monitoring

Monitoring of blood parameters for patients receiving evinacumab is not expected to differ from patients receiving comparator treatments. However, the monitoring cost is considered because patients receiving more effective therapies are likely to live longer. Since monitoring costs in HoFH were not available, monitoring costs applied in the model were obtained from NICE CG181 which have been applied in NICE appraisals TA385, TA393, TA394 and TA694. It has been recognised that lomitapide has the potential for hepatoxicity and requires heightened surveillance (85). This should include liver function tests (LFTs) every 3 months and annual liver imaging using Fibroscan®, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography. In the UK, Fibroscan is probably most widely used, at a bundled cost of £55 (HRG RD48Z, ultrasound elastography) (190). It should be noted that this is a conservative cost, as the consequences of a positive pathological result are not modelled. Progressive hepato-steatosis may trigger the need for further imaging modalities, consultations, drug adjustments, and ultimately drug cessation, as well as associated with consequent iatrogenic morbidity (e.g., development of cirrhosis).

A summary of the HCRU and unit cost estimates associated with monitoring are summarized in

Table 47 and Table 44. All costs were inflated to the 2020 price level using the most recent published PSSRU data (188).

Table 43. Cost related to monitoring of blood for evinacumab.

Resource use	Year 1	Subsequent years	Source	Costs	Source
Routine appointments					
Blood sample appointment	2	1	NICE CG181	£7.41	PSSRU 2021 (188)
GP appointment	2	2		£52.77	
Blood tests					
Total cholesterol	2	1	NICE CG181	£1.15	Assumptions, NICE TA385
HDL cholesterol	2	1		£1.15	
Liver transaminase (ALT or AST)	2	1		£1.15	
Total annual monitoring costs (first year)				£127.26	
Total annual monitoring costs (subsequent years)				£116.40	

Abbreviations: ALT. alanine transaminase; AST, aspartate aminotransferase; GP, general practitioner; NICE, national institute for care and health excellence.

Note: an additional annual cost of £55 is included for ultrasound elastography (lomitapide only).

Table 44. Cost related to monitoring of blood for lomitapide.

Resource use	Year 1	Subsequent years	Source	Costs	Source
Routine appointments					
Blood sample appointment	2	1	NICE CG181	£7.41	PSSRU 2021 (188)
GP appointment	2	2		£52.77	
Blood tests					
Total cholesterol	2	1	NICE CG181	£1.15	Assumptions, NICE TA385
HDL cholesterol	2	1		£1.15	
Liver function tests	4	4		£1.15	
Fibroscan	1	1	NHS National Tariff	£55.00	HRG RD48Z, ultrasound elastography
Total annual monitoring costs (first year)				£184.56	
Total annual monitoring costs (subsequent years)				£174.85	

Abbreviations: ALT. alanine transaminase; AST, aspartate aminotransferase; GP, general practitioner; NICE, National Institute for Care and Health Excellence.

Note: an additional annual cost of £55 is included for ultrasound elastography (lomitapide only).

B.3.5.5 Health-state costs

An economic systematic literature review was conducted in which economic studies in HoFH were sought (Appendix I). However, no studies were identified that report healthcare resource use (HCRU) and costs for the treatment people with HoFH. Thus, a targeted review of health state costs used in previous cost-effectiveness models in CVD was conducted. Priority was given to previous NICE technology appraisals. Health state costs used in previous HTA submissions and considered for use in this analysis are summarised in Appendix I, Table 15.

In the base case analysis, costs of health states reported in TA694 were used and inflated to reflect 2020 prices. These cost data were mainly derived from the study by Danese *et al.* (2016) (191), which reported on cost data concerning all the CV events of interest with the exception of stable angina. This was a retrospective cohort study using Clinical Practice Research Datalink (CPRD) records from 2006 to 2012 to identify individuals receiving LLT with their first and second CV-related hospitalisations (n=24,093). Identified subjects were linked to Hospital Episode Statistics (HES) data, and from these costs were estimated using tariffs attached to Healthcare Resource Groups (HRGs). A “a pre-post design”, using patients as their own controls, was implemented to reduce the influence of confounding. This study reported comprehensive cost data of suitable granularity to be implemented in the model, namely:

- Cost data for UA, MI, TIA and stroke (ischaemic)
- Cost data on primary and secondary CV events
- Cost data for the first 6 months post event, and annualised data thereafter

Danese *et al.* (2016) was selected for the base case as it included only patients receiving LLT and this patient group is especially relevant for the current analysis.

Health state cost for stable angina and post-stable angina was sourced from NICE clinical guidance CG181 on lipid modification as the cost for these health states was not available in Danese *et al.* (2016). In the guidance, a cost-effectiveness analysis was conducted for low-, medium-, and high-intensity statin treatment for the primary and secondary prevention of CVD. Costs of health states were based on estimates of resource use that a typical adult with corresponding CV condition would be expected to receive in line with NICE guidance and standard NHS practice.

The study by Walker *et al.* (2016) (192) was used to inform the cost of CV death. It reported on data from the The ClinicAl research using Linked Bespoke studies and Electronic Records (CALIBER) study (192). This study utilised linked data from (CPRD), the Myocardial Ischaemia National Audit Project (MINAP) registry, HES, and the Office for National Statistics (ONS).

Costs used in the base case analysis of the model are described in Table 45. Health state costs were applied to the model depending on which CV event has experienced (i.e., state occupancy). A separate cost was applied to the “acute” health states (i.e., the first 12 months within the event), and the post-event health states (i.e., longer-term management following the first 12 months) to reflect the increased HCRU requirements by patients shortly after

experiencing a CV event. If a patient has a subsequent CV event, the model assumed that costs for the first event would stop incurring and costs for the subsequent event would apply.

Table 45. Costs associated with health states.

Health state	Cost	Source
Stable angina	£8,002	NICE GC181
Post-stable angina	£248	NICE GC181
Unstable angina	£2,499	Danese *et al.* (2016)
Post-unstable angina	£386	Danese *et al.* (2016)
MI	£4,920	Danese *et al.* (2016)
Post-MI	£992	Danese *et al.* (2016)
Stroke	£4,256	Danese *et al.* (2016)
Post-stroke	£986	Danese *et al.* (2016)
TIA	£2,036	Danese *et al.* (2016)
Post-TIA	£820	Danese *et al.* (2016)
CV death	£239	Walker *et al.* (2016)

Abbreviations: CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack

B.3.5.6 Adverse reaction unit costs and resource use

Costs associated with the treatment of adverse events (AE) were not included in the model. This is because, the prevalence of severe treatment-related AEs associated with each treatment was factored in the model with an associated unit cost of each of these AEs. However, most of the severe AEs reported in the study of lomitapide and evinacumab referred to CV events, the impact of which has been captured already through health state costs. No other severe treatment-related AEs were reported regarding evinacumab and lomitapide. Hence, the prevalence of treatment-related severe AEs associated with evinacumab and lomitapide in the base case was assumed to be 0%. The same assumption was made for other background treatments as no differences were expected between the intervention and comparator arm.

B.3.5.7 Miscellaneous unit costs and resource use

The adoption of evinacumab would not require the addition of any services or infrastructure. As discussed in Section B.3.5.4 Cost of monitoring displacement of lomitapide would potentially remove the need for liver monitoring. Costs associated with annual imaging has been included for the comparator arm in the model, but costs associated with the consequences of long-term liver abnormalities, ranging from deranged LFTs to cirrhosis, have not been quantified due to a lack of informing data.

No societal cost was included in the base case. LDL apheresis is associated with significant opportunity cost for the NHS and considerable burden at the individual level, and

evinacumab could reduce the requirement for LDL apheresis in patients with HoFH. However, as the model base case assumed the same proportion of LDL apheresis reduction in patients treated with the intervention and comparator, potential reduction in productivity loss and caregiver burden were not included in the model.

B.3.6 Uncertainty

HoFH is an ultra-rare condition and consequently there are limitations in the evidence base in research areas such as prognosis (natural history of the disease) and the efficacy of treatment for the condition. There are five key areas in the evidence base relating to these that are a cause of uncertainty.

Firstly, there is uncertainty relating to the baseline risk of CV events (Section B.3.3.3.1 Time to . Whilst there is a considerable volume of literature describing the history of HoFH (see Section B.1.3 Health condition and position of the technology in the treatment pathway) studies accurately reporting on the incidence of CV events are lacking. Furthermore, such studies are inevitably confounded by the fact that participants received LLT related to the historical period the study was undertaken. The current model estimated the rate of CV events through extrapolation of CV deaths from the IPD of a historical cohort of patients from the pre-statin period (156). Whilst this allowed for flexibility in the model, with the effects of modern LLT being introduced separately and collectively, the underlying assumption of baseline risk was estimated from a small retrospective observational study with limited internal validity, which adds to the overall uncertainty in the model.

Secondly, the distribution of CV events was extrapolated from the risk of CV death using data derived from an SLR in people from the general population (157). This was a necessary assumption because this level of data granularity does not exist for people with HoFH. However, the study data is unlikely to accurately reflect the HoFH population, who are subject to the atherogenic process from a very young age, and as a result are at increased risk of conditions such as aortic stenosis (193), rather than diseases more represented in older age, such as TIA and stroke. This issue becomes particularly apparent in the model at younger ages, because age groups <40 years were not reported in the review by Ward *et al*. (2007), as CV events are rare in the general population below this age range.

Thirdly, as with previous models submitted to the NICE STA programme in this field (158, 160, 173, 178, 194), the efficacy of the drugs investigated were measured using the intermediate endpoint of LDL-C reduction. However, whilst the relationship between LDL-C events and circulating LDL-C concentration is well established in the general population (25, 177), this is not the case in individuals with severe FH or HoFH. In the model, the relative reduction in LDL-C mediated through LLT are translated into absolute reductions in LDL-C, which are used to calculate the reduction in risk of CV events. It is not clear whether the log-linear relationship persists in people with extremely high baseline levels of LDL-C (195). However, there was no way of mitigating against this uncertainty.

Fourthly, there is uncertainty arising from the internal validity of the trials used to inform the LLT efficacy. The ELIPSE study (5) was a double-blind randomised placebo-controlled trial judged to be at low risk of bias (Appendix D.4), which allows for confidence in its results. However, the pivotal trial for lomitapide was single-armed and had several methodological and reporting limitations (Section B.2.9.3 Pivotal study on lomitapide (Cuchel *et al.* 2013).

This study was assessed as being at high risk of bias, as well as confounding that could not be controlled for. Additionally, as there were no head-to-head data, an ITC was undertaken which caused additional issues relating to sample size and residual confounding (Section **Error! Reference source not found.** Uncertainty surrounding the relative efficacy of the intervention and comparator is tested with sensitivity analyses.

Lastly, there is uncertainty on the long-term efficacy of the drugs. In the model, the efficacy of the drugs is derived from the pivotal trials by mean of the ITC. Whilst there are data reporting the efficacy of evinacumab is long-lasting (Section B.2.4.2 Study R1500-CL-1719 (interim long-term safety and efficacy)), these interim data are not controlled and lack the internal validity of the DBTP data. The extended data of the lomitapide pivotal trial were difficult to interpret due to a high rate of patient attrition, which was not accounted for (107). Furthermore, long-term RWE data reported from the LOWER (86) and Pan-European (165) registries were also difficult to interpret due to retrospective nature of the research and the high rates of discontinuation observed. Thus, it was not possible to draw meaningful long-term comparisons between the intervention and the model in order to populate the model.

B.3.7 Managed access proposal

There is no proposal for a managed access scheme.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of the base case analysis inputs is reported in **Table 46**.

Table 46. Summary of variables applied in the economic model

Variable	Value	CI (distribution)
Discount rate: costs	3.5%	Not varied
Discount rate: outcomes	3.5%	Not varied
Time horizon	58 years	Not varied
Base case patient characteristics (at baseline) *Section **Error! Reference source not found.***		
Age	42 years	Not varied
Proportion female	54%	Not varied
Body weight (in log)	4.25kg	Lognormal (4.25, SD 0.26)
Proportion null/null mutation	32%	Beta (21, 44)
LDL-C level	8.71	Gamma (2.90, 3.00)
CV event baseline risks *Section B.3.3.3.1 Time to*		
Gompertz model (rate, shape)	-5.94, 0.06	Cholesky decomposition 0.0003728 | -0.010554368 -0.010554368 | 0.37572886
Distribution of CV events *Section B.3.3.3.2 Distribution of CV events*		
Distribution of CV events: male, 40-54, stable angina	0.31	Dirichlet (55,19,52,11,23,18)
Distribution of CV events: male, 40-54, unstable angina	0.11	Dirichlet (55,19,52,11,23,18)
Distribution of CV events: male, 40-54, MI	0.30	Dirichlet (55,19,52,11,23,18)
Distribution of CV events: male, 40-54, TIA	0.06	Dirichlet (55,19,52,11,23,18)
Distribution of CV events: male, 40-54, Stroke	0.13	Dirichlet (55,19,52,11,23,18)
Distribution of CV events: male, 40-54, CVD death	0.10	Dirichlet (55,19,52,11,23,18)
Distribution of CV events: male, 40-54, Total event rate per 1000 person per year	4.20	Not varied
Distribution of CV events: male, 55-64, stable angina	0.33	Dirichlet (39,9,21,11,25,16)
Distribution of CV events: male, 55-64, unstable angina	0.07	Dirichlet (39,9,21,11,25,16)
Distribution of CV events: male, 55-64, MI	0.17	Dirichlet (39,9,21,11,25,16)
Distribution of CV events: male, 55-64, TIA	0.09	Dirichlet (39,9,21,11,25,16)
Distribution of CV events: male, 55-64, Stroke	0.21	Dirichlet (39,9,21,11,25,16)
Distribution of CV events: male, 55-64, CVD death	0.13	Dirichlet (39,9,21,11,25,16)
Distribution of CV events: male, 55-64, Total event rate per 1000 person per year	13.70	Not varied

Distribution of CV events: male, 65-74, stable angina	0.21	Dirichlet (59,23,48,28,75,44)
Distribution of CV events: male, 65-74, unstable angina	0.08	Dirichlet (59,23,48,28,75,44)
Distribution of CV events: male, 65-74, MI	0.17	Dirichlet (59,23,48,28,75,44)
Distribution of CV events: male, 65-74, TIA	0.10	Dirichlet (59,23,48,28,75,44)
Distribution of CV events: male, 65-74, Stroke	0.27	Dirichlet (59,23,48,28,75,44)
Distribution of CV events: male, 65-74, CVD death	0.16	Dirichlet (59,23,48,28,75,44)
Distribution of CV events: male, 65-74, Total event rate per 1000 person per year	24.30	Not varied
Distribution of CV events: male, 75-84, stable angina	0.19	Dirichlet (31,13,26,13,56,23)
Distribution of CV events: male, 75-84, unstable angina	0.08	Dirichlet (31,13,26,13,56,23)
Distribution of CV events: male, 75-84, MI	0.16	Dirichlet (31,13,26,13,56,23)
Distribution of CV events: male, 75-84, TIA	0.08	Dirichlet (31,13,26,13,56,23)
Distribution of CV events: male, 75-84, Stroke	0.34	Dirichlet (31,13,26,13,56,23)
Distribution of CV events: male, 75-84, CVD death	0.14	Dirichlet (31,13,26,13,56,23)
Distribution of CV events: male, 75-84, Total event rate per 1000 person per year	37.50	Not varied
Distribution of CV events: male, 85-100, stable angina	0.21	Dirichlet (56,25,48,4,91,36)
Distribution of CV events: male, 85-100, unstable angina	0.10	Dirichlet (56,25,48,4,91,36)
Distribution of CV events: male, 85-100, MI	0.19	Dirichlet (56,25,48,4,91,36)
Distribution of CV events: male, 85-100, TIA	0.02	Dirichlet (56,25,48,4,91,36)
Distribution of CV events: male, 85-100, Stroke	0.35	Dirichlet (56,25,48,4,91,36)
Distribution of CV events: male, 85-100, CVD death	0.14	Dirichlet (56,25,48,4,91,36)
Distribution of CV events: male, 85-100, Total event rate per 1000 person per year	42.60	Not varied
Distribution of CV events: female, 40-54, stable angina	0.33	Dirichlet (29,11,7,14,21,8)
Distribution of CV events: female, 40-54, unstable angina	0.12	Dirichlet (29,11,7,14,21,8)
Distribution of CV events: female, 40-54, MI	0.08	Dirichlet (29,11,7,14,21,8)
Distribution of CV events: female, 40-54, TIA	0.16	Dirichlet (29,11,7,14,21,8)
Distribution of CV events: female, 40-54, Stroke	0.23	Dirichlet (29,11,7,14,21,8)
Distribution of CV events: female, 40-54, CVD death	0.09	Dirichlet (29,11,7,14,21,8)
Distribution of CV events: female, 40-54, Total event rate per 1000 person per year	1.60	Not varied
Distribution of CV events: female, 55-64, stable angina	0.35	Dirichlet (35,7,9,10,29,11)

Distribution of CV events: female, 55-64, unstable angina	0.07	Dirichlet (35,7,9,10,29,11)
Distribution of CV events: female, 55-64, MI	0.09	Dirichlet (35,7,9,10,29,11)
Distribution of CV events: female, 55-64, TIA	0.10	Dirichlet (35,7,9,10,29,11)
Distribution of CV events: female, 55-64, Stroke	0.29	Dirichlet (35,7,9,10,29,11)
Distribution of CV events: female, 55-64, CVD death	0.11	Dirichlet (35,7,9,10,29,11)
Distribution of CV events: female, 55-64, Total event rate per 1000 person per year	6.60	Not varied
Distribution of CV events: female, 65-74, stable angina	0.20	Dirichlet (43,11,26,15,81,36)
Distribution of CV events: female, 65-74, unstable angina	0.05	Dirichlet (43,11,26,15,81,36)
Distribution of CV events: female, 65-74, MI	0.12	Dirichlet (43,11,26,15,81,36)
Distribution of CV events: female, 65-74, TIA	0.07	Dirichlet (43,11,26,15,81,36)
Distribution of CV events: female, 65-74, Stroke	0.38	Dirichlet (43,11,26,15,81,36)
Distribution of CV events: female, 65-74, CVD death	0.17	Dirichlet (43,11,26,15,81,36)
Distribution of CV events: female, 65-74, Total event rate per 1000 person per year	12.40	Not varied
Distribution of CV events: female, 75-84, stable angina	0.15	Dirichlet (34,8,23,23,107,35)
Distribution of CV events: female, 75-84, unstable angina	0.03	Dirichlet (34,8,23,23,107,35)
Distribution of CV events: female, 75-84, MI	0.10	Dirichlet (34,8,23,23,107,35)
Distribution of CV events: female, 75-84, TIA	0.10	Dirichlet (34,8,23,23,107,35)
Distribution of CV events: female, 75-84, Stroke	0.46	Dirichlet (34,8,23,23,107,35)
Distribution of CV events: female, 75-84, CVD death	0.15	Dirichlet (34,8,23,23,107,35)
Distribution of CV events: female, 75-84, Total event rate per 1000 person per year	23.40	Not varied
Distribution of CV events: female, 85-100, stable angina	0.14	Dirichlet (11,2,8,7,42,12)
Distribution of CV events: female, 85-100, unstable angina	0.03	Dirichlet (11,2,8,7,42,12)
Distribution of CV events: female, 85-100, MI	0.10	Dirichlet (11,2,8,7,42,12)
Distribution of CV events: female, 85-100, TIA	0.09	Dirichlet (11,2,8,7,42,12)
Distribution of CV events: female, 85-100, Stroke	0.50	Dirichlet (11,2,8,7,42,12)
Distribution of CV events: female, 85-100, CVD death	0.15	Dirichlet (11,2,8,7,42,12)
Distribution of CV events: female, 85-100, Total event rate per 1000 person per year	32.90	Not varied
Risk of recurrence *Section B.3.3.4.1 Increased risk of subsequent cardiovascular events*		
RR in cardiac events due to previous events (UA, SA, MI)	1.50	Lognormal (1.5, 0.30)

RR in cardiac events (UA, SA, MI) due to previous events (stroke, TIA)	1.20	Lognormal (1.2, 0.24)
RR in cardiac events (Stroke, TIA) due to previous events (UA, SA, MI)	1.20	Lognormal (1.2, 0.24)
RR in cardiac events (TIA, stroke) due to previous events (TIA, stroke)	1.50	Lognormal (1.5, 0.30)
RR of CV death due to history of prior event	1.50	Lognormal (1.5, 0.30)
Background treatment mix *Section B.3.3.2.1 Background treatment mix*		
Atorvastatin	0.94	Beta (61,4)
Ezetimibe	0.75	Beta (49,16)
Evolocumab	0.77	Beta (50,15)
Lipoprotein apheresis	0.34	Beta (22,43)
Lomitapide	0.00	Not varied
Efficacy (% reduction in LDL-C) *Section B.3.3.5 Treatment efficacy*		
Atorvastatin	20.0%	Normal (0.200, 0.026)
Ezetimibe	20.7%	Normal (0.207, 0.042)
Evolocumab	30.8%	Normal (0.308, 0.066)
LDL apheresis	37.1%	Normal (0.504, 0.047)
Lomitapide	40.1%	Normal (0.401, 0.058)
Evinacumab	55.1%	Normal (0.551, 0.086)
Reduction of apheresis associated with treatment *Section B.3.3.7.2 LDL apheresis discontinuation*		
Atorvastatin/ezetimibe/evolocumab	0%	Not varied
Lomitapide	16%	Beta (4, 25)
Evinacumab	16%	Beta (4, 25)
Treatment discontinuation *Section B.3.3.7 Treatment discontinuation*		
Lomitapide (short-term)	14%	Beta (4, 25)
Lomitapide (long-term)	0%	Not varied
Atorvastatin/ezetimibe/evolocumab (short-term)	0%	Not varied
Atorvastatin/ezetimibe/evolocumab (long-term)	0%	Not varied
CV event risk reduction due to 1mmol/L change in LDL-C *Section B.3.3.3.3 Alternate sources of baseline CVD* risk During the development of the model, other sources of baseline risk were considered for use in the base case or scenario analyses. Both were primary CVD risk assessment algorithms, namely the Framingham Risk Score (FHS) (171) and the QRISK3 algorithm (172). The FHS is a predictive CVD risk algorithm used to estimate the 10-year probability of CVD events. It was developed based on a cohort of individuals from the general population (without a history of CVD) aged 30 to 74 years from Framingham, Massachusetts. However, the generalisability of this algorithm has been previously heavily		

criticised in TA394, as the derivation cohort was based on a single-centre study of otherwise healthy individuals, and did not reflect the high-risk population of that assessment (173). For this reason, this source of baseline CVD risk was discarded.

The QRISK tool was originally developed in 2007 (174). It is used to estimate a person's 10-year risk of developing a heart attack or stroke, based on UK general population aged 25 to 84 years without previous CVD events. The tool has undergone three iterations, with the latest version being QRISK3 (175). The QRISK tool has been previously recommended in NICE CG181 as the preferred method for risk scoring for primary prevention of CVD (162). The QRISK tool has also been used within the context of cost-effectiveness modelling in NICE, with TA385 using these source data (160).

A major limitation of applying QRISK3 to estimate CVD risk in HoFH is that this cohort of patients have very high levels of LDL-C, approximately 4 to 8 times higher compared with the general population (41). Therefore, as with the Framingham Risk Score and other similar predictive algorithms, it may not accurately predict CVD risk for HoFH patients, as in this context, HoFH patients could be statistical outliers. Additionally, CVD risk equations derived from non-FH populations are also likely to underestimate the CV risk patients with HoFH, due to the prolonged increase in LDL-C these patients experience, starting in childhood. The limitations and applicability of the QRISK3 tool has been identified in a previous NICE appraisal (160). Additionally, KOLs concurred that QRISK3 was not an appropriate source of data to estimate CVD risk in people with HoFH. For these reasons, its use was rejected, and instead HoFH specific data were applied, as reported in Thompson *et al.* (2015) (156).

B.3.3.4 LDL-C and risk of CV events

Stable angina	1.00	Not varied
Unstable angina	0.76	Lognormal (-0.27444, 0.02015)
Myocardial infarction	0.76	Lognormal (-0.27444, 0.02015)
TIA	1.0	Not varied
Stroke	0.85	Lognormal (-0.16252, 0.02720)
CVD death	0.88	Lognormal (-0.12783, 0.02042)
Drug acquisition costs per pack *Section B.3.5.1 Drug acquisition costs*		
atorvastatin	1.42	Not varied
ezetimibe	1.67	Not varied
evolocumab	340.20	Not varied
apheresis	1,526.26	Not varied
lomitapide	17,765.00	Not varied
evinacumab 345 mg	[redacted]	Not varied
Health state costs *Section B.3.5.5 Health-state costs*		

Stable angina	8,001.87	Gamma (61, 130)
Post-stable angina	248.25	Gamma (61, 4)
Unstable angina	2,499.03	Gamma (2362, 1)
Post-unstable angina	385.97	Gamma (26, 15)
MI	4,920.09	Gamma (2591, 2)
Post-MI	991.73	Gamma (53, 19)
Stroke	4,256.01	Gamma (1666, 3)
Post-stroke	986.25	Gamma (14, 71)
TIA	2,035.61	Gamma (856, 2)
Post-TIA	820.10	Gamma (31, 27)
CV death	238.94	Gamma (61,4)
Monitoring costs *Section B.3.5.4 Cost of monitoring*		
Monitoring cost: first year	127.26	Gamma (61, 2)
Monitoring cost: subsequent years	116.40	Gamma (61, 2)
Administration costs		
Atorvastatin/ezetimibe/evolocumab/lomitapide	0.00	Not varied
Evinacumab	504.00	Gamma (61, 9)
Health state utility *Section B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness* analysis		
Stable angina	0.62	Beta (403, 252)
Post-stable angina	0.78	Beta (600, 174)
Unstable angina	0.62	Beta (403, 252)
Post-unstable angina	0.78	Beta (600, 174)
MI	0.62	Beta (403, 252)
Post-MI	0.74	Beta (393, 137)
Stroke	0.63	Beta (101, 60)
Post-stroke	0.67	Beta (457, 227)
TIA	0.76	Beta (189, 60)
Post-TIA	0.76	Beta (204, 65)

B.3.8.2 Assumptions

A list of assumptions used in the model is reported in Table 47.

Table 47. List of assumptions used in the base case.

	Model input and cross reference	Source/assumption	Justification
Baseline CV risks	CV event reduction causally linked to LDLC-level. B.3.3.4 page 126	The rationale of the model is based on LDL-C reduction, as a surrogate outcome reduction in CV events	There is strong evidence that reducing LDL-C levels reduce CV events (8, 35, 39); this assumption has been accepted in previous NICE appraisals (40-44).
	Baseline CV risk Kaplan-Meier analysis of IPD using Thompson et al. (2015) (37) B.3.3.3 p121	Thompson 2015 cohort is representative of UK HoFH patients CV risk, in terms of patient characteristics, background treatment mix, and post-(background)treatment LDL-C values	Thompson 2015 provides a good source of baseline CV-risk data for UK HoFH patients as CV risk estimates estimated based on this study are disease and country specific. Alternative sources of empirical data may lack generalisability to the UK setting (9, 45). Thompson et al. (2015) reports data with sufficient granularity (i.e., IPD) to model time to CV death. Risk algorithms, such as Framingham Risk Score and QRISK are derived from the general population and cannot be generalised to HoFH (B.3.3.3, page 136)
	Extrapolation of time to death to time to first MACE. Thompson et a. (2015) (37) B.3.3.3.1 page 121	Assumption that time to death reported in the Thompson et al. (2015) IPD reflects time to first fatal-MACE for patients who had the outcome of death recorded in the IPD	In the absence of IPD from Thompson 2015 to model time to first MACE or time to first fatal MACE, this assumption was necessary. This is supported by the study authors who state " in the manuscript "the age of the first MACE in Dead patients averaged 23.4 ± 9.8 years; in many instances these events were post-operative and often fatal. The mean age of the first MACE in Alive patients was similar, 23.2 ± 8.2 years, but obviously none were fatal".
	Distribution of CV events Ward et al. (2007) (38) B.3.3.3.2 page 122	The rate and distribution of non-fatal CV events is inferred by applying non-fatal to fatal CV-event risk ratios, and non-fatal CV event distributions based on Ward et al 2007. The latter study is based on the UK general population, and an assumption is made that these rates are relevant for HoFH patients	Similar assumptions have been accepted in previous NICE appraisals in which patients with high CV risks were modelled. In the absence of data to model the risk of specific non-fatal CV events over time, there are no other sources of data to inform time-dependent rates for CV events captured by the model health states.

	Model input and cross reference	Source/assumption	Justification
	Distribution of CV events in younger people Ward et al. (2007) (38) B.3.3.3.2 page 123	It is assumed that the distribution of CV-events as reported by Ward et al (2007) in men and women of 45 to 54 years old, applies to all younger ages.	This was a necessary assumption due to a lack of data. This assumption has been accepted in previous NICE appraisals in people with FH.
Baseline LDL-C and treatment efficacy	Baseline LDL-C Thompson et al. (2015) (37) B.3.3.2.2 page 119	Baseline LDL-C prior to treatment (and post-background treatment) was assumed to be 8.71 mmol/L taken from Thompson et al. (2015) IPD. This is estimated by assuming changes in TC are attributed only to changes in LDL-C, and by applying methods to impute missing LDL-C values.	As the model captures changes in CV risk through the absolute reduction of LDL-C from baseline, it was considered appropriate for baseline LDL-C values to correspond to the same patient cohort from which baseline CV risks were derived, that is, Thompson et al. (2015) (37).
	Background treatment effect ELIPSE trial (18) B.3.3.2.1 page 119	The baseline LDL-C values were adjusted to account for the difference between the modelled treatment mix and the treatment mix corresponding to the baseline CV risk cohort (i.e., Thompson et al. 2015 (37)). These adjustments were applied by applying treatment effects (removing or adding) weighted by the difference in the percentage of patients receiving each treatment between the modelled treatment mix and that reported Thompson et al. (2015) (37).	Adjustments to the baseline LDL-C to reflect different treatment mix were considered necessary to reflect the impact of a different treatment mix on the risk of CV events. This also gave the model the flexibility to test other management assumptions.
	Long-term efficacy B.3.3.5 page 128	Changes in LDL-C captured by the clinical studies in the shorter term are assumed to be maintained over lifetime	This was a necessary assumption in the absence of long-term data. This assumption has been previously made and accepted in multiple NICE appraisals in which CV events were modelled. This may be a conservative assumption in that the true benefits of reduced exposure to LDL-C over time may not be fully accounted for.
	Increased risks from secondary CV events B.3.3.4.1 page 127	The CV death risk post-event state is adjusted by a relative risk of 1.5 to reflect the increased probability of CV events in all post-event health states, and a relative risk of 1.2 to	There is empirical evidence that the risk of death in survivors of a recurrent MI is 1.5 times higher than that for survivors of a first MI.

	Model input and cross reference	Source/assumption	Justification
		reflect increased probability of cardiac events (SA, UA, MI, CV-death) following a cerebral event (TIA, stroke, CV-death, and vice versa.	This assumption was made in NICE TA694 (44) and NICE TA393 (42).
	Cessation of LDL apheresis following treatment Cuchel et al. (2013) (29) B.3.3.6.2 page 132	Apheresis reduction is associated with both evinacumab and lomitapide and assumed to be equal.	There is evidence related to lomitapide that has shown that there is a percentage of patients on lomitapide who can discontinue apheresis due to well-controlled LDL-C levels. It was assumed in the model that since evinacumab is expected to show improvements in efficacy compared with lomitapide, evinacumab is also expected to be non-inferior in terms of apheresis reduction due its LDL-C lowering effects.
Cost assumptions	Costs over time B.3.5 page 138	Health state costs for both the acute CV-event health states and the post-event health states are assumed to be constant over time.	This assumption is necessary and in line with previous NICE appraisals.
	Treatment intensity	The base case treatment intensity is 100% for evinacumab and other treatments.	In absence of treatment intensity levels for other comparator treatments, 100% treatment intensity is considered to be a conservative assumption that can be tested in sensitivity analysis.
	Administration costs (relating to intravenous route) B.3.5.2 page 139	Administration costs are applied only to patients in evinacumab.	Evinacumab is administered via the intravenous route, while lomitapide, ezetimibe, and statins are taken orally. For evolocumab, most patients are assumed to self-administer the treatment via self-injection. Hence, no administration costs were applied for comparator treatments. This assumption has been accepted previously by the NICE ERG in the evolocumab submission (43).
	Patient adherence	100% patient adherence is assumed for all treatments.	This assumption was applied and accepted in NICE TA385 (41). This is a conservative assumption that may not reflect adherence issues that could occur with lomitapide use in particular.
Utility assumpt	Utility values for CV events in HoFH are the same as the general population B.3.4.5 page 135	Health state utilities based on the general population who have experienced CV events are assumed to be equivalent to utilities of HoFH patients. This assumes that HoFH has	There are no HoFH specific utility data which can be used in the model. This may be a conservative assumption as the long periods of time that HoFH patients experience increased LDL-C levels

	Model input and cross reference	Source/assumption	Justification
		no direct impact on patients' utility but rather indirect impact through an increased probability of experiencing these events.	may lead to more severe CV events on average compared with the general population and therefore lower utility values.
	Age adjustment B.3.4.5 page 135	Utilities are age-adjusted by assuming the same rate of change due to age as in the general population	This assumption is in line with previous NICE TAs and is considered standard practice
	Evinacumab administration	No disutility is assumed related to the administration mode and frequency of evinacumab.	There is no data to inform this factor. However, the frequency and length of administration of evinacumab are not expected to have a significant impact on patients' utility.
	Disutility for treatments. B.3.4.4 page 134	LDL apheresis has been associated with disutility using treatment-disutility of haemodialysis as a proxy. All other treatments were assumed to have no treatment-related impact on utility	In absence of direct, quantitative evidence to show that evinacumab, lomitapide and other orally administered comparators are associated with disutility, this was assumed to be 0 in the model. However, this was likely to be a conservative assumption, considering the AE profile of lomitapide. Data on apheresis-related disutility was not available in the literature, therefore, treatment-disutility of haemodialysis was used as a proxy for apheresis. Haemodialysis is provided on average 3 times a week for 3-5 hours (assuming 4 as the average) and has a disutility value of -0.164 (185). Apheresis is provided in the model once every two weeks and is carried out for 2 to 3 hours (assuming 2.5 hours as the average).

Abbreviations: CV, cardiovascular; IPD, FH, familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; individual patient data; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; SA, stable angina; UA, unstable angina.

B.3.9 Base-case results

Base-case results were presented in the form of incremental cost-effectiveness ratio (ICER), capturing the incremental costs per QALY. The base case analysis was conducted for a lifetime horizon. A confidential price discount of [redacted] per 345mg vial of evinacumab) was applied (as agreed with NHSE). In line with the NICE reference case, a discount rate of 3.5% per year was applied for both costs and benefits for future years. Results of the deterministic base case base analysis are presented in Table 48. Results of base case broken down by categories, namely treatment acquisition costs, monitoring costs, health state costs, LYs and QALYs are provided in Table 49.

As shown in the tables, evinacumab combined with SoC was dominant compared to lomitapide combined with SoC. It implied that evinacumab combined with SoC generated more QALYs at a lower net cost over a lifetime. In addition, there is a positive net monetary benefit associated with evinacumab combined with SoC.

Table 48. Base-case results

	Total			Incremental				
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	**INMB (£)**
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	5,955,254	12.84	10.05	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

Table 49. Summary of disaggregated results of the base-case analysis.

Outcomes	Technology		Incremental
	Evinacumab + SoC	Lomitapide + SoC	
Costs			
Drug costs	[redacted]	£5,938,073	[redacted]
Monitoring costs	£1,537	£1,500	£37
Health state costs	£13,125	£13,292	-£167
CV death costs	£2,296	£2,389	-£93
Total costs	[redacted]	£5,955,254	[redacted]
Health outcomes			
Life years	[redacted]	12.84	[redacted]
QALYs	[redacted]	10.05	[redacted]

Abbreviations: CV, cardiovascular; QALYs, quality-adjusted life years; SoC, standard of care.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

B.3.10.1.1 Methods

A probabilistic sensitivity analysis (PSA) was conducted to describe how uncertainty around input parameters was translated into uncertainty around the estimated outputs of the model. Suitable probability distributions were assigned to model parameters to characterise the uncertainty around mean values of model inputs. The type of distribution was selected based on the type of parameter. Beta distribution was used for transition probabilities and utility values, gamma distribution for costs, log-normal distribution for ratios. Choleskey decomposition was used to adjust the baseline risk prediction in the survival analysis of CV risks. The distributions of parameters are reported in Table 46.

A probabilistic value was assigned to each parameter in an iterative process. The process was repeated for 5,000 times, and the results of each of these iterations were used to determine the distribution of incremental costs and incremental QALYs.

B.3.10.1.2 Results

The results of the PSA for the comparison between evinacumab and lomitapide are presented within a cost-effectiveness plane in the form of a joint distribution of costs and QALYs, along with a mean value of the ICER and a 95% confidence interval ellipse, in Figure 28. The probability that each treatment is cost-effective and results in the highest net monetary benefit is presented over different values of the cost-effectiveness threshold in the form of a cost-effectiveness acceptability curve (CEAC) in Figure 29.

The input parameters (Table 46) were included in the PSA. Parameters which were not expected to materially impact on the ICER (e.g., rate of AEs) were not varied in the PSA. The results of the base case PSA are reported in Table 50Table 52. . The results of the PSA disaggregated by cost category are reported in Table 51.

Table 50. Base-case probabilistic results.

	Total			Incremental				
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	**INMB (£)**
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	6,028,419	13.02	10.18	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

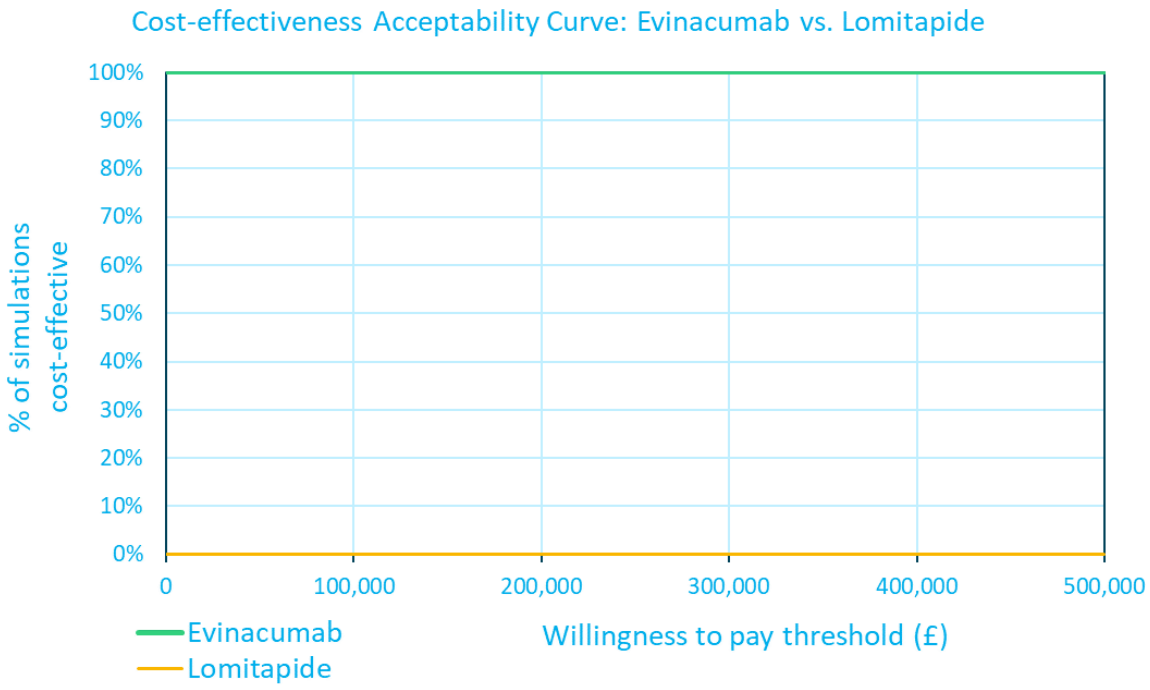
Table 51. Summary of disaggregated results of the probabilistic base-case analysis.

Outcomes	Technology		Incremental
	Evinacumab + SoC	Lomitapide + SoC	
Costs			
Drug costs	[redacted]	£6,011,310	[redacted]
Monitoring costs	£1,553	£1,519	£34
Health state costs	£13,098	£13,275	-£177
CV death costs	£2,230	£2,315	-£84
Total costs	[redacted]	£6,028,419	[redacted]
Health outcomes			
Life years	[redacted]	13.02	[redacted]
QALYs	[redacted]	10.18	[redacted]

Abbreviations: CV, cardiovascular; QALYs, quality-adjusted life years; SoC, standard of care.

Figure 28. Cost-effectiveness plane and scatter diagram.

Figure 29. Cost-effectiveness acceptability curve.



B.3.10.2 Deterministic sensitivity analysis

B.3.10.2.1 Methods

A one-way deterministic sensitivity analysis (DSA) was conducted to establish those parameters with the greatest impact on the model's results. To determine the parameters to which the model was most sensitive to, each parameter was set a lower and upper value while other parameters remained constant.

Upper and lower values of model parameters were determined by the 95% CI where available or estimated by varying the standard error by ±1.96 times. When no information on the variation around the mean value of a parameter was available, the values used in the univariate sensitivity analysis were estimated by varying the mean value of the parameter by 25%.

B.3.10.2.2 Results

The results for sensitivity analyses were presented in terms of incremental net monetary benefit (INMB). The ICER are not used since these can be difficult to interpret, and potentially misleading, when presented without additional context of incremental costs and incremental QALYs. The INMB is calculated using a cost-effectiveness threshold of £30,000, and positive values indicate that evinacumab is cost-effective; conversely a negative value shows evinacumab is not cost-effective, in that instance.

Results of the DSA are reported in tabular format in Table 52, and presented as a Tornado diagram in Figure 30. This indicates the 10 parameters with the greatest influence on the

INMB in a descending order; that is, it identifies the parameters the model is most sensitive to.

Table 52. Deterministic sensitivity analysis results.

Parameter	INMB - at lower value of parameter (£)	INMB - at upper value of parameter (£)
Demographics: Cohort baseline age (11.6, 72.4)	4,580,915	1,332,977
Baseline risk: Gompertz (Thompson *et al.* (2015)) Rate (-4.45, -7.42)	1,870,418	4,038,714
Baseline risk: Gompertz (Thompson *et al.* (2015)) Shape (0.04, 0.07)	3,547,800	2,365,702
Demographics: Patient weight - Log mean (4.10, 4.30)	3,244,256	2,793,830
Discontinuation short-term: Lomitapide (0.10, 0.17)	3,140,932	2,694,465
Demographics: baseline LDL-C level imputed (Thompson *et al.* (2015)) (3.5, 16.9)	2,760,292	3,112,098
Efficacy: LDL-C proportional reduction (Lomitapide) (0.29, 0.51)	2,795,904	3,025,909
Patient % of vial acceptable underdose (0%, 30%)	2,917,698	3,144,453
RR in cardiac events due to previous events (UA, SA, MI) (1.00, 2.09)	3,008,348	2,837,806
Efficacy: LDL-C proportional reduction (Evinacumab) (0.38, 0.72)	2,992,214	2,855,757

Abbreviations: INMB, incremental net monetary benefit; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RR, relative risk; SA, stable angina; UA, unstable angina.

Figure 30. Tornado diagram

Abbreviations: INMB, incremental net monetary benefit; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; OWSA, one-way sensitivity analysis; RR, relative risk; SA; stable angina; UA, unstable angina.

B.3.10.3 Scenario analysis

B.3.10.3.1 Methods

A range of scenarios were tested using scenario analyses. These 13 scenarios are listed in Table 53, with the accompanying rationale for their consideration.

Table 53. Summary of scenario analysis inputs.

Number	Scenario	Base case	Alternative assumption (s)	Rationale
1	Alternative efficacy for apheresis in LDL-C reduction	37.1%	50.4% (Pottle *et al.* (2019))	Test the impact of alternative data source
2	Lower patient body weight	72.7	60.0kg	To evaluate the impact of a lower mean body weight on the results
3	Assume for evinacumab no unused vial wastage	Full wastage, i.e., no vial sharing	No wastage, i.e., allow vial sharing	A conservative assumption of no vial sharing was made for evinacumab in the base case. Drug acquisition cost therefore included a cost of drug wastage. This scenario assessed the impact of this assumption on cost-effectiveness results
4	Evinacumab administration frequency	Monthly	Once every 4-week	To evaluate the impact of alternative administration frequency for evinacumab
5	Underdosing for evinacumab	Assumed no underdosing	Up to 20% underdosing based on target weight	In clinical practice, underdosing may happen when to incur the cost of a full further vial. This scenario was included to evaluate the impact of underdosing.
6	Alternative of survival function	Gompertz	Log-logistic	Test the impact of alternative parametric function used in the survival analysis
7	Alternative utility source	Those used in TA694	Those used in TA385	Test the impact of alternative data source

8	Alternative cost source	Those used in TA694	Those used in TA385	Test the impact of alternative data source
9	Evinacumab discontinuation	0%	50% of that of lomitapide	Test the impact of evinacumab discontinuation
10	Alternative link between 1mmol/L LDL-C change and CV rate reduction	CTTC 2015	Navarese *et al.* (2015)	Test the impact of alternative data source
11	Alternative link between 1mmol/L LDL-C change and CV rate reduction	CTTC 2015	Navarese *et al.* (2018)	Test the impact of alternative data source
12	Alternative discount rate for both costs and utility values	3.5%	1.5%	Explore alternative discount rate for costs and outcomes
13	Alternative evinacumab efficacy	55.1%	50.9%	Test the impact of alternative data source
Abbreviations: CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.				

B.3.10.3.2 Results

The results of the scenario analyses are reported in

ID	Scenario	Incremental costs	Incremental QALYs	INMB (£)	Relative change from base-case INMB (%)
-	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Apheresis efficacy LDL-C reduction 50.4% (Pottle *et al.* (2019))	[redacted]	[redacted]	[redacted]	-0.6%
2	Patient lower mean body weight of 60kg	[redacted]	[redacted]	[redacted]	11.6%
3	Assume for evinacumab no unused vial wastage	[redacted]	[redacted]	[redacted]	12.8%
4	Evinacumab given on 4-weekly rather than monthly basis	[redacted]	[redacted]	[redacted]	-8.3%
5	Evinacumab underdosed up to 20% based on target weight	[redacted]	[redacted]	[redacted]	5.2%

6	Choice of survival function: Log-logistic distribution	[redacted]	[redacted]	[redacted]	27.5%
7	Alternative utility source: TA395	[redacted]	[redacted]	[redacted]	0.0%
8	Alternative cost source: TA395	[redacted]	[redacted]	[redacted]	0.1%
9	Evinacumab discontinuation 50% of lomitapide	[redacted]	[redacted]	[redacted]	6.6%
10	Link between 1 mmol/L LDL-C change and CV rate reduction alternative source (Navarese *et al.* (2015))	[redacted]	[redacted]	[redacted]	8.6%
11	Link between 1 mmol/L LDL-C change and CV rate reduction alternative source (Navarese *et al.* (2018))	[redacted]	[redacted]	[redacted]	-4.6%
12	Assuming 1.5% discount rate for costs and utilities	[redacted]	[redacted]	[redacted]	25.9%
13	Evinacumab efficacy 50.9% (ELIPSE RCT vs placebo with lomitapide patients removed)	[redacted]	[redacted]	[redacted]	0.6%

Abbreviations: CV, cardiovascular; INMB, incremental net monetary benefit; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; RCT, randomised controlled trial.

Cells shaded green indicated evinacumab is cost-effective in this scenario cells shaded in red indicate evinacumab is not cost-effective in this scenario.

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Table 54. Results of the base case analyses.

ID	Scenario	Incremental costs	Incremental QALYs	INMB (£)	Relative change from base-case INMB (%)
-	Base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Apheresis efficacy LDL-C reduction 50.4% (Pottle *et al.* (2019))	[redacted]	[redacted]	[redacted]	-0.6%
2	Patient lower mean body weight of 60kg	[redacted]	[redacted]	[redacted]	11.6%
3	Assume for evinacumab no unused vial wastage	[redacted]	[redacted]	[redacted]	12.8%
4	Evinacumab given on 4-weekly rather than monthly basis	[redacted]	[redacted]	[redacted]	-8.3%
5	Evinacumab underdosed up to 20% based on target weight	[redacted]	[redacted]	[redacted]	5.2%
6	Choice of survival function: Log-logistic distribution	[redacted]	[redacted]	[redacted]	27.5%
7	Alternative utility source: TA395	[redacted]	[redacted]	[redacted]	0.0%
8	Alternative cost source: TA395	[redacted]	[redacted]	[redacted]	0.1%
9	Evinacumab discontinuation 50% of lomitapide	[redacted]	[redacted]	[redacted]	6.6%
10	Link between 1 mmol/L LDL-C change and CV rate reduction alternative source (Navarese *et al.* (2015))	[redacted]	[redacted]	[redacted]	8.6%
11	Link between 1 mmol/L LDL-C change and CV rate reduction alternative source (Navarese *et al.* (2018))	[redacted]	[redacted]	[redacted]	-4.6%
12	Assuming 1.5% discount rate for costs and utilities	[redacted]	[redacted]	[redacted]	25.9%
13	Evinacumab efficacy 50.9% (ELIPSE RCT vs placebo with lomitapide patients removed)	[redacted]	[redacted]	[redacted]	0.6%

Abbreviations: CV, cardiovascular; INMB, incremental net monetary benefit; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; RCT, randomised controlled trial.

Cells shaded green indicated evinacumab is cost-effective in this scenario cells shaded in red indicate evinacumab is not cost-effective in this scenario.

B.3.11 Subgroup analysis

Economic subgroup analyses, as defined by the decision (Table 1), was not undertaken, as it was considered unfeasible for the following reasons:

- People aged 12 to 17 years inclusive: lomitapide is not indicated for this subgroup. There are currently no comparative or published evinacumab data in this population, with evidence being restricted to single-armed data (Section B.2.7.4 Use in adolescent patients). Additionally, the efficacy of background treatments, where indicated, in this population is limited.
- Presence or level of risk of cardiovascular disease: all patients with HoFH are considered to be at high risk of CV disease. In practice, treatment is not stratified by cardiovascular risk but by attainment of LDL-C target levels (Section B.1.3.6 Patient management pathways). These are rarely achieved, regardless of prior history of CV events.
- Mutational status (e.g., LDLR status, compound heterozygotes, double heterozygotes): evinacumab is effective in all patients with HoFH, regardless of the underlying genetic mutation. This is also true for lomitapide, so the differential effect between these drugs in the model is expected to be minimal. In clinical practice, treatment of HoFH is guided by underlying LDL-C levels, not mutational status. In the model, the lack of efficacy of statins and evolocumab are modelled by including a proportion of patients who have no response to these drugs (Section B.3.3.2.1 Background treatment mix However, whilst the proportion of null/null patients can be adjusted, this may be misleading as they do not necessarily reflect the population of the trials they are based on.

B.3.11 Validation

B.3.11.1 Internal validation

An internal structured quality-check procedure for cost-effectiveness models was undertaken with the full involvement of the principal developer and a senior economic modeller, the latter of whom was not directly involved in the project.

As specified by the quality check procedure, once the model was completed a series of diagnostic tests will be performed to confirm that all calculations and programming are correct, and the model is applying all formulae correctly. These diagnostic tests add to the general validation of the logic and results of the model, which is achieved by performing different scenario analyses. A sample of indicative steps of the quality-control process are described below:

- Set all comparator treatments to have the same treatment effect and costs. This test demonstrates that the treatment arms have the same logic and calculations and hence will conclude to the same results with the same data
- Check that the number of patients at all stages of the model always sums to the number of patients entering the model. This test ensures that patients are neither entering nor leaving the model (only changing from one state to another)
- Set all costs to 0 and check that the cost of both treatments is 0 for every year. This test demonstrates that all the costs are derived from the values in the "Costs" sheet and that without these (i.e., with them set to £0) the cost of each treatment strategy is £0
- Set all utility values to 1 and check that the number of life-years (LYs) each year is the same as the number of QALYs. This test demonstrates that all patients alive are being counted in the LY gained and QALY calculations

B.3.11.2 External validation

No cost-effectiveness studies in this disease area were identified by the SLR (Appendix G). However, a study was found that allows a validation of the baseline risk modelling to be performed.

An important area of uncertainty associated with the cost-effectiveness model is the survival function for time to CV-death. This was estimated using data for the cohort presented in the Thompson *et al.* (2015) study (156). The strengths of this source include it being from a UK centre and in the target patient population, however, its limitations include the relatively small sample size and the long observation window.

The study by Leipold *et al.* (2017) (196) estimated the survival benefit resulting from a change LDL-C concentration assumed to occur with lomitapide. This study constructed survival functions for time to CV-death using data on patients published in the study by Raal *et al.* (2011) (170). It is possible to approximately replicate the Leipold *et al.* (2017) analysis using the cost-effectiveness model and to compare the results from the two approaches to modelling baseline risks.

The study by Leipold *et al.* (2017) presented results for a range of different scenarios; however, for the purpose of this comparison, focus was placed on treatment initiated at age 18 years and using the CTTC (2010) (25) as the source for CV risk reduction following a change in LDL-C concentration. The change in mean survival in this scenario was found to be 4.7 years. In order to attempt to replicate this scenario, the following modifications were made to the cost-effectiveness model:

- Patient starting age set to 18 years
- Discount rates for costs and benefits set to 0%
- Comparator set to SoC, such that evinacumab is an add-on treatment
- All background therapies removed, such that no adjustments are made to the starting LDL-C concentration

- Efficacy of evinacumab set to 38%, to match the efficacy of lomitapide assumed in the Leipold *et al.* (2017) study
- Rate ratio for CV-death set to 0.8 per mmol/L reduction in LDL-C, to match the value used in the Leipold *et al.* (2017) study

Applying these changes results in an estimated survival benefit of 4.2 years, compared to 4.7 years reported in the Leipold *et al.* (2017) study. There are other differences between the approaches that could contribute to the different outputs, in particular the methods of modelling time to first MACE. This comparison indicates that the model for baseline risks applied in this cost-effectiveness model may imply health benefits that are conservative, relative to the approach used in the Leipold *et al.* (2017) study.

B.3.14 Interpretation and conclusions of economic evidence

An economic model was developed using the cost-utility analysis framework that was fully consistent with the NICE reference case (148). The model was derived from the seminal work of Ara *et al.* (2008) (161) which has been used as the basis for several previous NICE HTAs (158, 160, 173, 178, 194) on LLT in FH or other causes of hyperlipidaemia. However, this is the first HTA undertaken by NICE on a technology intended to extend life and improve HRQoL in people with HoFH, and as such, has presented its own unique challenges. The disease of HoFH is complex, and, mainly due to its low prevalence, evidence can be limited and difficult to interpret. Although every attempt was made to reduce uncertainty in model results (reported fully in Section B.3.6 Uncertainty, it was recognised that some weaknesses in the evidence base and model assumptions could not be avoided. To mitigate against this, extensive sensitivity analyses were undertaken to understand the nature of the uncertainty and to inform decision makers (Section B.3.10 Exploring uncertainty.

In the base case, the model found that the use of evinacumab in addition to fully optimised standard of care was associated with modest gains in the number of life years [redacted]) and QALYs gained ([redacted] compared with treatment with lomitapide. However, evinacumab was associated with large cost savings, equating to over [redacted] GBP over the model lifetime per person. Thus, evinacumab dominated lomitapide. When PSA was undertaken, nearly all simulations were in the southeast quadrant (and all were cost-saving). The CEAC indicated that the probability that evinacumab was cost-effective was approximately 100%, up to a willingness-to-pay threshold of £500,000 per QALY gained. Furthermore, evinacumab remained cost-effective in all the univariate DSAs undertaken, with the key drivers of the model being related to the unit costs of the comparator drug (lomitapide), the starting age of the cohort, and assumptions concerning the baseline risk of CV events. Scenario analysis indicated that evinacumab remained dominant in all the situations tested.

Experimental evidence from the ELIPSE trial has clearly demonstrated that evinacumab is highly effective at reducing LDL-C in people with HoFH (5), with reductions of around 50% reported, whether ITC data (Section **Error! Reference source not found.** or naïve data are used (Section B.2.6.1 Changes in LDL-C levels (primary endpoint), and also irrespective of patient characteristics, underlying mutations, or background treatment (Section **Error! Reference source not found.**. There is considerable confidence in these results as ELIPSE was a placebo-controlled trial assessed as being at low risk of bias (Appendix D.1). In contrast, the efficacy of lomitapide is more modest, at around -40.1% as reported in the

pivotal trial (108). However, this data is less certain and at higher risk of bias, owing to the limitations of the trial, principally because it lacked a comparator group. Nevertheless, the superior efficacy of evinacumab translated into only limited lifetime QALY gains in the model. This was due to the incremental nature of treatment for HoFH, with treatment algorithms being additive and treatment effects being cumulative. Thus, although evinacumab demonstrates materially greater superiority in efficacy compared with all other forms of LLT, including LDL apheresis, evolocumab and lomitapide, its placement as last-line in the base case of the model patient pathway meant its overall effect was modest incrementally, compared with lomitapide.

It should be considered that the diminishing returns with regard to treatment effect accrued from multiple forms of LLT may be regarded as somewhat arbitrary. The key observation is that LDL-C targets are not achieved despite using all currently available treatment, leaving significant unmet need (Section B.1.3.9 Unmet needs). The need for additional effective treatment is widely recognised as central in the management of HoFH (2). This fundamental requirement for treating HoFH is underlined by the fact that some current options are recommended despite being invasive and having significant indirect costs (LDL apheresis, Section B.1.3.8.2 LDL apheresis), or being poorly tolerated and having an unfavourable AE profile (lomitapide, Section B.1.3.7.4 Lomitapide If LDL apheresis were displaced as a treatment in favour of the more recent pharmacological options, as recommended by the most recent EAS consensus guidelines (4), this would increase the benefits of evinacumab by placing it earlier in the treatment pathway (Section B.1.3.6 Patient management pathways Figure 8). With all things being equal, evinacumab is cost-effective in the treatment of HoFH compared with lomitapide, dominating its comparator by offering improved efficacy at a reduced cost. However, evinacumab has other key advantages that the model does not fully account for.

Evinacumab has so far demonstrated a favourable safety profile, which is highlighted by the trial data showing few participants discontinuing treatment (5, 121), and none related to AEs. Evinacumab is effective at reducing LDL-C regardless of patient demographics, comorbidities, background treatment, or mutational status. This means that for those most severely affected by HoFH; people who are null-null for LDLR function and in whom statins and evolocumab are ineffective, are likely to gain the most benefit from evinacumab, with the drug having the greatest absolute effect on LDL-C in this cohort. Whilst this may also be true of lomitapide, this drug exhibits greater variability of response and so far there has been insufficient data to conclude it is effective in all subgroups (165). Importantly, evinacumab has a broader indication than lomitapide, being suitable for use in adolescents (12 to 17 years inclusive) and people who are contraindicated to, or cannot tolerate, lomitapide. In particular, adolescents represent a population with a particular unmet need. This group may further benefit through the early introduction of treatment, potentially reducing the cumulative exposure to atherogenic lipids, that is, treating according to the universally applied maxim “the sooner the better” (197), which is particularly true in people at very high risk of CVD (195).

In summary, it has been conclusively demonstrated that evinacumab has the potential to improve outcomes and reduce costs in the management of people with HoFH, as well as having several other important advantages over its currently available comparator,

lomitapide. This warrants its adoption into the NHS as a critical life-saving treatment for people with HoFH.

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B.5 List of appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
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- C1.2 UK public assessment report

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Appendix H: Health-related quality-of-life studies
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Summary of Information for Patients (SIP)

May 2023

File name	Version	Contains confidential information	Date
ID2704_evinacumab summary of information for patients_26052023_no ACiC	1.0	No	26/05/2023
ID2704_evinacumab summary of information for patients_09062023_V2_no ACiC	2.0 (as per request)	No	09/06/2023

ID2704_evinacumab summary of information for patients_23062023_V3_no ACiC	3.0 (as per request)	No	23/06/2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Evinacumab Brand name: EVKEEZA®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults and adolescents, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Evinacumab was given a marketing authorisation* by the Medicines and Healthcare products Regulatory Agency (MHRA)** in August 2022.

* a marketing authorisation is a license that allows a drug to be given to patients because the drug has been judged to work and is safe based on clinical trials.

** The MHRA are the group responsible for giving the marketing authorisation to drugs

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Collaboration with Genetic Alliance UK

Purpose of Activity: Ultragenyx has not supported this organisation directly however it supported its Rare Day 2023 collaboration with ITN (International News Network). They produced 'Together Caring for Rare Disease' which launched on 28th February 2023 online. The programme looked at how rare disease can be complex and life limiting, often with a long diagnostic journey and delayed treatment. Advanced technology, genetic science, treatment, and management - together caring for rare disease - can make all the difference. It was available online on Rare Disease Day and supported by a marketing campaign led by Genetic Alliance UK targeting its members and an advertising digital campaign ran by ITN Business. The Ultragenyx section included a 3-minute video on HoFH which focused on disease education and awareness. The video included interviews with the General Manager of Ultragenyx UK, Ireland & Nordics, a clinician and the CEO of Heart UK.

Financial Support: As part of the agreement with ITN, Ultragenyx paid £19,750 to ITN for the UK filming. The money is paid to ITN and not to Genetic Alliance UK. Ultragenyx was one of several company supporters for 'Together Caring for Rare Disease'.

Collaboration with Heart UK

Purpose of the activity: HEART UK 36th Annual Medical & Scientific Conference - For medical, scientific, healthcare, and student attendees with an interest in lipids, atherosclerosis, cholesterol conditions, cardiovascular disease, and nutrition and involved in primary and secondary care or industry. Ultragenyx is a 'Partner' level sponsor/exhibitor and as such can have 2 stand representative places/conference registrations and a stand.

Financial Support: £4,000 + VAT

Collaboration with FH Europe, a network patient organization dedicated to improving Europe-wide awareness, understanding, and access to diagnosis and treatment of inherited lipid conditions

Purpose of Activity: Ultragenyx worked with FH Europe on the development and rollout of a Quality-of-Life Survey aiming to capture the quality of life of people with HoFH and or their caregivers. FH Europe provide input to the development of the survey and assistance in its dissemination to people living with HoFH via the FH Europe membership network.

Financial Support: 3,875 GBP

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Homozygous familial hypercholesterolemia (HoFH) is a very rare, inherited, serious, life-long disease. It causes cholesterol to build up in the body to very high levels. One type of cholesterol is called low-density lipoprotein cholesterol (LDL-C), which is sometimes called the "bad" form of cholesterol. High levels of LDL-C are dangerous because they increase the risk of cardiovascular problems (issues with the heart and blood vessels), such as heart attacks, angina, stroke, and heart failure. In HoFH, these issues can happen from a very young age (1). Scientific research has shown that even in children with HoFH as young as 7 years, significant LDL-C build up in the arteries can occur. There is also a higher risk of death at a young age, with people as young as 18 years dying of the condition if it is left untreated (2). HoFH is a genetic disease and is passed down through both parents. It affects 1 person for every 250,000 people worldwide (3) and has been estimated to affect 1 person for every 1 million people in the United Kingdom (UK) (4). However, there are thought to be people with HoFH who are not diagnosed so this number could be higher. Around 50 to 60 people receive treatment for HoFH in the UK.

Research has shown that HoFH can negatively impact the lives of people with HoFH and their families. A major reason for this impact is because of incidents such as heart attacks and strokes (4). These sorts of events are life-changing for patients, both physically, because people may have problems in performing usual day-to-day activities that were once an important part of their life, and mentally, because of the fear an event may happen again. Family members, friends or other voluntary carers may also suffer because of the additional physical support they need to give and the anxieties that the person they know with HoFH may have another event.

Research has overall shown that for people with HoFH, there is an increased risk of anxiety and depression (5). Other findings from research have shown a negative impact on self-perception, feelings of being devalued, and stigmatisation. There is also a negative impact on education and employment. This negative impact may be caused by tiredness from HoFH, the time spent in hospital and the intensity of some current treatments. For instance, LDL-apheresis is a medical procedure that filters blood through a tube to remove the excess cholesterol. Many patients in the UK receive this treatment and it can have a significant burden due to the physical demands of the procedure and the risks involved with repeated access to the veins. Additionally, LDL-apheresis treatment involves travel-related commitments to and from hospital every week or every two weeks, with 2-3 hours at a time on the machine (5). This can make it particularly difficult in people living in more remote regions of the country.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

There are a number of processes used by medical professionals to make a diagnosis of HoFH. This may be guided through physical signs of someone having the disease, including xanthomas (visible deposits of cholesterol under the skin), xanthelasma (yellow growth near the eyelids), or corneal arcus (a white or blueish ring or arc in the eye caused by cholesterol) (6). A blood test may also be carried out to see if cholesterol levels are high. Questions about family history are also asked. This is usually focused on whether another family member has ever had any form of familial hypercholesterolaemia (FH) or any heart problems. Genetic testing is also carried out for those with likely or definite FH, to fully confirm the diagnosis and assess the exact genetic type of HoFH

the person has (7). People with very faulty copies of the low-density lipoprotein receptor (LDLR) gene (sometimes called "null/null") have the most severe disease and have a poor response to some drugs, particularly statins and proprotein convertase subtilisin/kexin type 9 (PCKS9) inhibitors such as evolocumab.

Evinacumab is a new treatment for HoFH that NICE are currently assessing. There will be no additional diagnostic tests needed in order to give evinacumab to patients.

2c) Current treatment options:

In order to manage HoFH, different treatments are needed to lower cholesterol. Because HoFH leads to very high levels of LDL-C, it is almost always necessary to give a combination of treatments to reduce cholesterol, especially LDL-C. These are given in steps (sometimes called "lines of treatment") with more treatments added depending on the person's response to previous treatment(s) and how it makes them feel (side effects). A brief overview of these treatments is explained below. Figure 1 further highlights the treatment pathway and shows the point where the new drug, evinacumab, would be introduced to patients following other treatments.

As an initial first-step approach in the management of HoFH, the implementation of *lifestyle modifications* is recommended. This includes maintaining a healthy weight and physical activity, alcohol moderation or restriction, and stopping smoking. This is encouraged for all people with HoFH, to maintain cardiovascular health, but its impact on LDL-C levels is limited (4). Drug treatments are always needed as well, and these are prescribed as follows:

First-line treatment: statins

Statins are given to nearly all people with HoFH from a young age (8). Statins are a family of drugs that are given to lower cholesterol levels and risk of cardiovascular events in wide range of people. People with HoFH are often given the highest dose that they are able to tolerate (called "high-intensity treatment"). Statins prescribed in HoFH include simvastatin, atorvastatin, and rosuvastatin. Generally, statins are well-tolerated with few serious side effects; however, they can be ineffective in some HoFH patients who lack cholesterol receptors (LDLR). For people with HoFH who have up to 30% of LDLR activity (known as being receptor-defective), the average level of LDL-C reduction is 26% from baseline (the level of cholesterol without treatment). However, this average cholesterol reduction is only 15% in patients without functioning receptors (known as being receptor-deficient) (4, 9).

First/second line treatment: ezetimibe

Ezetimibe is given to nearly all people with HoFH from a young age. It works by reducing cholesterol absorption and is therefore often given alongside statins as a "first-line" treatment, as the two drugs work well with each other. Like statins, ezetimibe is well tolerated but can be limited in how effective it is in reducing LDL-C levels in people with HoFH with LDLR deficiency (10). When given with statins, a reduction in LDL-C of around 15 to 20%, compared with levels before treatment, may be expected (11).

Second line treatment: evolocumab

Evolocumab is part of a class of drugs called PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors drugs, which are a newer type of therapeutic approach (medicine) known as monoclonal antibodies (like evinacumab). These are proteins that are made in laboratories that can stop the normal function of a protein in the body called PCSK9. By stopping this protein, this can lower cholesterol in the body. Evolocumab is the name of the PCSK9 inhibitor typically prescribed in the UK for HoFH. It is recommended that evolocumab is tried in people who are taking statins and ezetimibe, but their cholesterol levels are still too high. However, a limitation of PCSK9 inhibitors is that they rely on cholesterol receptors (LDLR) in the body to work. This means for people with HoFH who have little to no function of their receptors, evolocumab is ineffective, and treatment will be stopped (4). Evolocumab is given as a jab just beneath the skin (subcutaneous injection) which can usually be administered by the patient themselves. In patients who respond to it, a reduction in LDL-C of about 30% may be expected (12).

Third line treatment: lomitapide

Lomitapide is currently the last drug treatment option given for HoFH and is only prescribed when all other treatments have been tried (statins, ezetimibe, evolocumab, and LDL apheresis) but cholesterol levels are still higher than what they should be (not at target). Lomitapide works by directly inhibiting an enzyme in the liver that makes cholesterol. It is different to the other drug treatments because it does not rely on cholesterol receptors (LDLR), meaning that even for patients with very limited or no receptors, it can still help to reduce cholesterol levels. Lomitapide is taken orally in the form of a capsule or capsules every day. Research has shown that lomitapide can be effective in reducing cholesterol compared with other treatments that are given earlier on in the pathway, reducing LDL-C by about 40% (13).

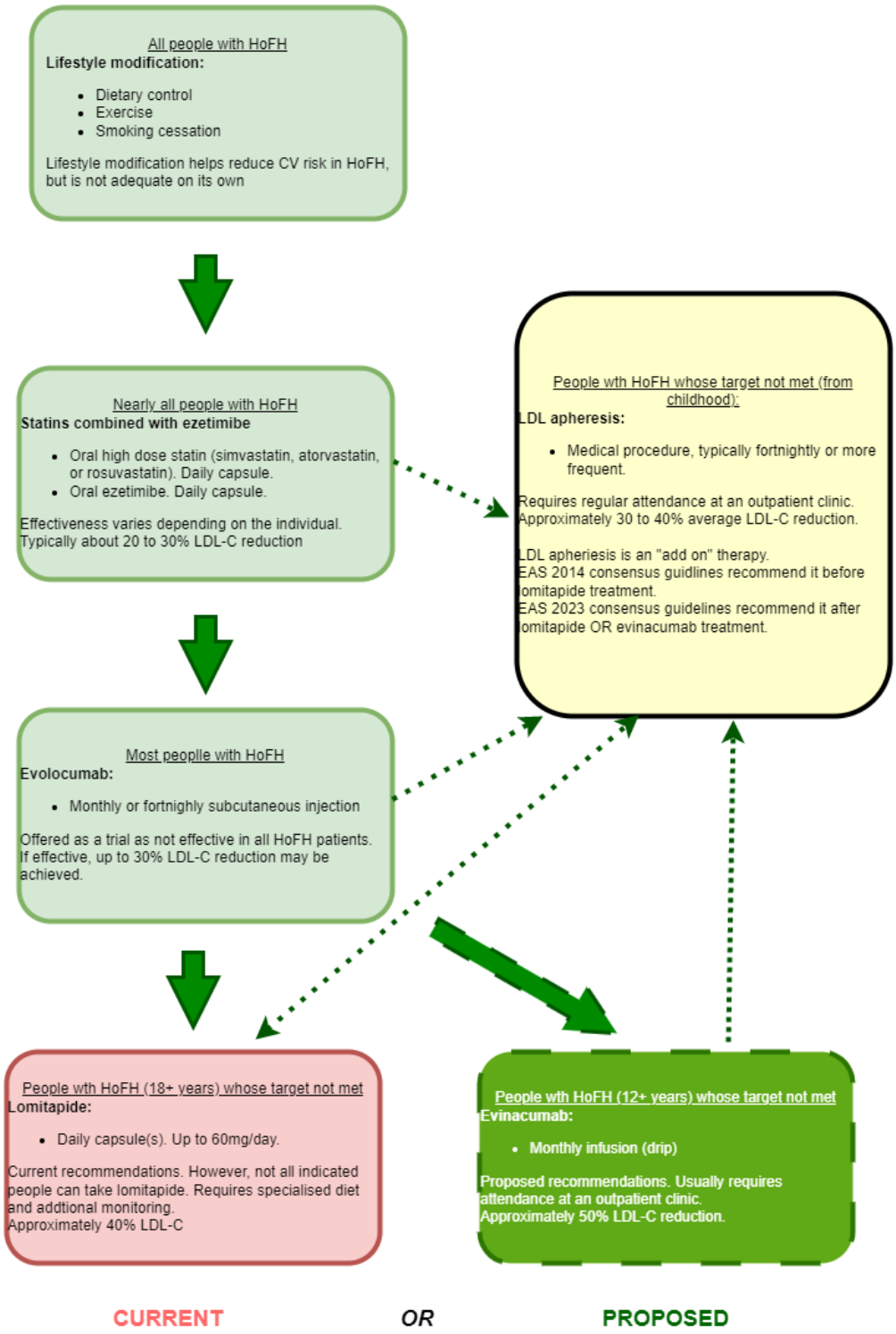
Unlike the first- and second-line treatments explained above, there are some limitations to using lomitapide. Firstly, lomitapide cannot be given to people with HoFH under the age of 18 years, unlike statins and ezetimibe. Secondly, lomitapide has side effects and requires a strict diet which not all people can adhere to. Although it is recommended that all people with HoFH should restrict their intake of fat in their diet, taking lomitapide requires people to be stricter, ensuring fat makes up less than 20% of energy intake, which can be difficult for some people. They will also need to abstain from alcohol and take additional dietary supplements (14). Possible side effects include nausea and diarrhoea, which can be worsened if this diet is not followed. Thirdly, lomitapide causes fats to build up in the liver so the dose of lomitapide that can be taken has to be carefully controlled. This will mean extra blood samples need to be taken and additional monitoring with ultrasound or other imaging diagnostics is recommended once a year (14). Finally, lomitapide can interfere with other drugs, such as statins, so additional care may be taken when prescribing these together.

LDL-apheresis*

LDL-apheresis is a procedure by which blood is filtered through a machine to physically remove the excess LDL-C. LDL-apheresis may be given alongside drug treatments when these are not lowering LDL-C levels enough (before or after lomitapide is tried). LDL-apheresis is effective at reducing cholesterol levels in people with HoFH for short periods of time with reductions of up to 70% observed following the procedure (15). However, the LDL-C rapidly builds back up so in the longer term, average reductions of between 30% and 40% are usual (16, 17). A major issue with LDL-apheresis is that the treatment is invasive (requiring needles and blood tubes) and requires people (and potentially their carers) to frequently travel every week or 2 weeks to a specialist

hospital clinical. As there are only a limited numbers of hospitals in the UK where this is available, it can involve lengthy travel times and be disruptive to life. Depending on the severity of HoFH, the procedure can last 2 to 3 hours at a time, with additional medical monitoring also needed, due to risk of infection, the potential impact on blood pressure, and reduction in blood calcium and iron (anaemia).

Figure 1. UK treatment pathways for people with HoFH with proposed position for evinacumab.



*Recently recommended treatment guidelines that have been developed by specialist doctors in HoFH were published in May 2023 (18). These guidelines recommend that LDL-apheresis is given as a last option to patients following all drug treatments (so after lomitapide or evinacumab). Because these guidelines are so new, they are not yet used in practice but by moving LDL-apheresis as a last option, this will reduce the burden on patients and carers caused from this type of treatment.

2d) Patient-based evidence (PBE) about living with the condition

A research study in collaboration with FH Europe (see section 1d) is currently ongoing. The aim of the study is to gather data on the quality-of-life of people with HoFH, and those who care for people with HoFH. This data is being collected through an on-line survey. The survey asks some general questions about the patient's/caregiver's background, diagnosis of HoFH, if the patient is on a special diet, and any details of LDL-apheresis treatment (including how that affects the patient or the carer in terms of time and money cost). The survey also contains a questionnaire called the EQ-5D which asks general questions about quality of life. The survey was launched first in English and will be translated into further languages. As data collection and analysis is ongoing, the initial responses will be used to inform the company's submission to NICE for evinacumab (results to be given in early June 2023) and the final results, which will include even more survey responses, are expected to be published in late 2023/ early 2024.

SECTION 3: The treatment

3a) How does the new treatment work?

Evinacumab is a new innovative medicine that has been given regulatory approval (licenced) in Europe and the UK (19). It is part of a newer group of drugs known as a recombinant human monoclonal antibody, which are modified versions of molecules that originally worked in the immune system. Scientists have engineered it to specifically bind with a protein in the body, called angiopoietin-like protein 3 (ANGPTL3), which regulates cholesterol. The body mainly produces this protein in the liver, and it plays a prominent role in the regulation of fat metabolism by stopping other proteins, called enzymes (known as lipoprotein lipase and endothelial lipase) which break down and remove cholesterol from the blood. Thus, by blocking the action of ANGPTL3, evinacumab increases the breakdown and removal of cholesterol from the blood, lowering LDL-C levels. This lowers the risk of cardiovascular disease, such as heart attacks and strokes (20).

Evinacumab works in a different way to other cholesterol lowering drugs as it does not affect cholesterol receptors (LDLR). This means that it will work in all people with HoFH, and will *add* additional benefit above that of other drugs such as statins, ezetimibe, and evolocumab. It can also be used with LDL-apheresis.

3b) Combinations with other medicines

Evinacumab does not have to be taken with other medicines (that is, it is taken as what we refer to as a monotherapy). However, it will usually be given when other treatments have not been effective enough to control LDL-C levels. These drugs may include some or all of statins, ezetimibe, and evolocumab, and these treatments would continue as before. Evinacumab can also be used with LDL-apheresis. It is not expected that evinacumab would be used with lomitapide.

3c) Administration and dosing

Because it is a monoclonal antibody, evinacumab cannot be taken orally (by mouth). Instead, evinacumab has to be given as a drip (intravenous infusion), so is usually given in a hospital outpatient setting (although there is a chance that in the future, it could be given at home if the patient chooses). It needs to be given once per month over about a 60 minute period. Evinacumab is supplied in 345 mg vials. The dose of evinacumab depends on the patient's bodyweight and is set at 15 mg/kg of bodyweight. There are very few restrictions on who can take evinacumab and there are no changes to dosing needed in people who are elderly or who have liver or kidney problems (19).

3d) Current clinical trials

There are two completed (21, 22) and one ongoing clinical trial (23) in which evinacumab has been used to treat patients with HoFH. A summary of these trials is reported in Table 1.

Table 1. A summary of completed or ongoing trials relating to evinacumab.

Study Name and code	Phase	Location	Patient Characteristics	Number of Patients	Treatments Used	Timeframe
ELIPSE (NCT03399786) (22)	3	Multinational (11 countries)	People (aged ≥12 years) with HoFH	65	Evinacumab versus placebo	Jan 18 – Mar 20
R1500-CL-1331 (NCT02265952) (21)	2	Multinational (3 countries)	People (aged ≥18 years) with HoFH	9	Evinacumab	Feb 15 – Jul 18
R1500-CL-1719 (NCT03409744) (23)	3	Multinational (12 countries)	People (aged ≥12 years) with HoFH	116	Evinacumab	Mar 18 – May 23 (Estimate)

The ELIPSE trial (R1500-CL-1629, NCT03399786) was a multinational study carried out between January 2018 and March 2020 to collect data on the safety and effectiveness of evinacumab in individuals with HoFH (22). Sixty-five participants were randomised to receive evinacumab or placebo (a liquid containing no medicine) over a 24-week period, whereby treatment identity was withheld from both the clinical staff and patients until after this time (known as the double-blind treatment phase, DBTP). Following this, a second 24-week treatment period was carried out, whereby all participants were assigned to evinacumab and made aware of this. This was known as the open label treatment phase (OLTP). Data from the OLTP has not yet been published.

Trial R1500-CL-1331 (NCT02265952) was a multinational study carried out between February 2015 and July 2018, whereby 9 participants received single or multiple doses of evinacumab to collect data on the safety and effectiveness in individuals with HoFH (21). Both the clinical staff and patients were aware of their assigned treatment. This was one of the first studies of evinacumab in humans ("proof of concept") and different doses were used.

Trial R1500-CL-1719 (NCT03409744) is an ongoing, multinational study which commenced in March 2018. Its aim is to determine the long-term safety and efficacy data of evinacumab in 116

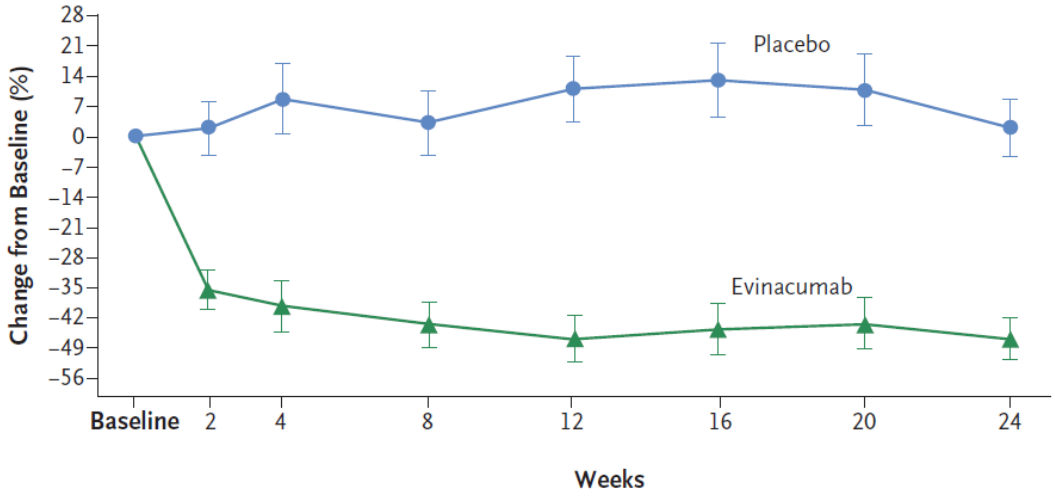
individuals with HoFH (23). Participants include those from NCT03399786 (ELIPSE) and NCT02265952, as well as new patients. Because this trial is ongoing, most of its results have not yet been published.

3e) Efficacy

The most important outcome of interest on trials of treatments for conditions related to hypercholesterolaemia (high cholesterol) is the level of LDL-C, as most treatments being studied are designed to reduce this. LDL-C is known as an intermediate or surrogate endpoint, as it is closely linked to the final outcome of interest, which is reduction in cardiovascular events (e.g., heart attacks, angina, and stokes). However, these events cannot be measured directly because of the small numbers of patients who are recruited into HoFH trials (because of its rarity) and the limited timeframes involved in clinical trials.

The ELIPSE trial is known as the "pivotal" trial of evinacumab in HoFH, as it was used to obtain marketing authorisation (that is, to become licensed so it is available to health services). It was relatively large in patient number, was of high quality (low risk of bias), and, most importantly, it had a control arm (patients having placebo). In stage 1 (DBTP) of the ELIPSE trial (Table 1), individuals with HoFH were treated with either evinacumab or a placebo, and the effectiveness of the two treatments were compared (22). The main outcome of interest was the impact of each treatment on the level of LDL-C in the blood. Data from the ELIPSE trial showed that after 24 weeks of treatment, evinacumab reduced LDL-C levels in the body by 49% on average, compared with placebo (22). Evinacumab was equally effective in people with HoFH irrespective of their genetic diagnosis or the other background treatments they were receiving at the same time. The effect of evinacumab on LDL-C levels reported in the ELIPSE trial is shown in Figure 2.

Figure 2. Graph showing reduction of LDL-C (main outcome of ELIPSE trial) over time in treatment and placebo patient groups.



Data reported from the other clinical trials supported the results of ELIPSE trial. In the R1500-CL-1331 trial, LDLC-C was reduced by an average of 49% after 4 weeks compared with baseline (21). The interim results (results before the trial is fully completed) from the R1500-CL-1719 study reported evinacumab reduced LDL-C at 24 weeks by 43.7% overall (81 participants), by 42.6% in adult patients (72 participants), and by 52.4% in adolescent patients (9 participants) (23). The principal limitation of these studies was that, unlike the ELIPSE trial, the data were not compared

with a control group. For all the studies, it should be borne in mind that LDL-C is, what we call, an intermediate outcome, not a clinical outcome, so there is inevitably some uncertainty in the benefits of the drug. Additionally, because HoFH is a rare disease, the number of patients enrolled into the trials were relatively few, which causes uncertainty in the precision of the outcomes, and the long-term effectiveness of the drug remains unanswered.

There are no studies that have directly compared the effectiveness of evinacumab with other treatments used to treat the condition. However, when naïve comparisons are made (that is, looking at raw data between studies), evinacumab has been observed to be at least as effective as lomitapide and almost certainly more effective than statins, ezetimibe, evolocumab, or LDL-apheresis. For reference, the pivotal trial for lomitapide reported a reduction in LDL-C of 40.1% at 26 weeks compared with baseline (24). The pivotal trial for evolocumab reported a reduction in LDL-C of 30.9% compared with placebo at 12 weeks (12). The data for ezetimibe and statins are older; however, one trial reported a reduction of 27.5% in LDL-C when a combined regimen of ezetimibe and high-intensity statins were compared with baseline at 12 weeks (11). Interpretation of the effectiveness of LDL-apheresis is also hindered by only poor quality evidence being available, but average reductions are likely to be between 30% and 40% in most patients (17).

3f) Quality of life impact of the medicine and patient preference information

As well as the ongoing quality-of-life survey study described in section 2d above, the ELIPSE trial (main pivotal trial), collected data from the EQ-5D questionnaire (generic quality-of-life questionnaire). Patients were asked to complete the questionnaire when they entered the trial and then again 24 weeks later. The data did not really demonstrate a meaningful change in quality-of-life, but this may have been due to two reasons.

Firstly, the questionnaire asks patients to think about the previous 24 hour period when considering their quality of life, and in a condition like HoFH where patients can have good days and bad days, there is the chance that the questionnaire may be given on a good day when they entered the trial, so the more negative impacts of the condition may not have been captured. Similarly, there is a chance the questionnaire may have been given on a bad day at the 24-week timepoint, so the positive impacts of treatment may not have been captured.

Secondly, HoFH is considered to be mainly an asymptomatic condition, because having high levels of LDL-C in itself does not normally make the person feel ill. However, cardiovascular disease arising from the high LDL-C levels (e.g. heart attacks, strokes) can have a very large negative impact on quality-of-life. However, because the trial was too short to detect these events, their effect on quality of life was also not detected.

3g) Safety of the medicine and side effects

During stage 1 of the ELIPSE trial (DBTP), the treatment-emergent adverse events (TEAEs) experienced by individuals treated with either evinacumab or a placebo were compared, which allows for the detection of adverse effects (commonly called side effects) likely to be caused by the drug. However, because the number of participants in ELIPSE was relatively low, even with a control group, only common side effects can be identified. A total of 29 patients (65.9%) in the evinacumab treatment group and 17 patients (81.0%) in the placebo treatment group experienced at least 1 TEAE. No patients experienced a TEAE leading to death or discontinuation of study treatment. Two patients (4.5%), both in the evinacumab treatment group, experienced 1 serious TEAE (SAE) each. However, upon investigation, neither of these events were considered to be related to evinacumab itself (22). The only TEAEs that were considered to be due to evinacumab were related injection site issues of flu-like symptoms, but these were mild in nature and did not require the patient to stop treatment. A similar reassuring safety profile was reported by patients in the proof-of-concept study (21).

One other, larger randomised controlled trial has been conducted on evinacumab in patients with a different type of hypercholesterolaemia (25). The safety results from this study are relevant to patients with HoFH. In this study, 272 people were randomised, with 238 receiving evinacumab. Of these 238 people, 28 people received the same dose of intravenous evinacumab (15 mg/kg) as in ELIPSE. There were no significant differences between treated groups or placebo in terms of overall TEAEs, and no deaths reported in any of the arms. The only TEAE that was considered to be due to evinacumab and required discontinuation was an allergic reaction to the drug (anaphylaxis) following a second dose of treatment. The patient made a full recovery.

In summary, the current trial evidence suggests that evinacumab is a safe drug. The only serious side effect so far detected was an allergic reaction, which can occur with any drug, especially when administered through a drip. However, because evinacumab is given in a hospital setting, this should reduce the risk of serious harm as specialist doctors and nurses will be there to closely monitor the individual. Because evinacumab is a new drug, it will remain under intensive monitoring by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for a period of time (26).

3h) Summary of key benefits of treatment for patients

HoFH is a serious life-long condition (Section 2a) caused by very high levels of LDL-C and consequently a much increased risk of cardiovascular disease. No single treatment is effective in reducing LDL-C to 'normal' levels, and for most people with HoFH, safe levels of LDL-C are not achieved even with multiple treatments (13). Therefore, evinacumab is intended as an addition to current treatments and not as a replacement, with the exception of lomitapide.

Evinacumab has the following key benefits which support its use in the healthcare system for the management of people with HoFH.

- It is highly effective at reducing cholesterol, with evidence from a high-quality placebo controlled clinical trial showing it reduces LDL-C by 49% (22). This is a high reduction rate when you look at reductions from other treatments in HoFH.

- Evinacumab can be used in combination with any other drug or LDL apheresis, having an additional effect (22). This means that the addition of evinacumab offers the best chance of a person with HoFH achieving relatively safe LDL-C levels
- Evinacumab works in a way that is not dependent on cholesterol receptors (LDLR). This works differently to evolocumab, statins, and to a lesser extent, ezetimibe. People with the most severe form of HoFH (null/null) achieve the least benefit from these treatments and have the most unmet need, which can be addressed with evinacumab
- LDL apheresis is associated with loss of quality of life (27). Evinacumab may allow for some patients to stop treatment with LDL apheresis. In the ELIPSE trial after 24 weeks treatment, only 23% of the evinacumab patients met eligibility criteria for LDL apheresis, compared with 77% receiving placebo (22)
- Evinacumab has several advantages over lomitapide. Namely, naïve data suggests it is more effective at reducing LDL-C (13, 22), it does not require a special diet, it has fewer side effects, and it does not interact with other drugs used in HoFH treatment. Importantly, evinacumab is available for use in adolescent patients who have a particular unmet need.

The ELIPSE trial has reported that 6 times as many people achieved strict LDL-C targets on evinacumab as people receiving placebo (data on file). However, even with evinacumab, LDL-C levels remained above optimal in most people. This highlights the requirement for continued vigilance for this condition and the need to use maximal treatment for HoFH, of which evinacumab is a crucial addition.

3i) Summary of key disadvantages of treatment for patients

There are few disadvantages associated with treatment with evinacumab. The main disadvantage is that treatment must be administered monthly by intravenous (IV) therapy (on a drip), which is an invasive procedure as it involves the insertion of a needle into a vein to allow direct delivery of evinacumab into the bloodstream. For most people, this will mean attending a hospital outpatient department once a month (although it is recognised that some patients may like to travel to hospital because it is an opportunity to meet other patients going through similar experiences). An evinacumab infusion is more convenient than LDL apheresis, which requires more frequent and longer attendances at highly specialised centres but may be less convenient than other treatments which are self-administered at home, either orally (by mouth) in the case of statins, ezetimibe, and lomitapide, or subcutaneously (skin injection) in the case of evolocumab. There is a chance that patients could choose to have their evinacumab infusion at home in the future and there is work currently going on in the background to assess how best this could work for patients and nursing arrangements.

Evinacumab is a new drug and, because of this, its long-term effectiveness and safety are not fully understood. However, there are currently no concerns regarding this based on the current research.

3j) Value and economic considerations

To be approved for use in the healthcare system, new treatments not only have to prove they are clinically effective, but also that they are cost-effective, meaning that as well as benefitting patients, they also offer value for money within the healthcare system. To do this, the company who has developed the treatment makes a cost-effectiveness model, which is sometimes also called a health economic model. This uses different methods to work out both the health benefits and costs of using evinacumab over a lifetime, as well as for the drug evinacumab is to be given instead of over time, which is lomitapide. Health benefits are measured in something called quality-adjusted life-years (QALYs) which measure not just how long life is prolonged with the treatment, but also the quality of that extended life. Costs include all costs associated with treatment, not just the costs of drugs, and include costs of blood tests or scans, as well as treating conditions caused by HoFH like heart attacks. Then using the QALY and cost values, another single value is calculated, which is known as an ICER (incremental cost-effectiveness ratio), which is the cost associated with each additional QALY gained.

<u>Model description</u>

A "state transition" (Markov) model was designed that captured the benefits and costs of using evinacumab in addition to the standard treatments (statins, ezetimibe, evolocumab and LDL apheresis) over the course of a lifetime (up to 100 years). The model did this by calculating the number of cardiovascular events (heart attacks, strokes, angina, and deaths) a person with HoFH (18 years and older) is likely to have each year, and how much evinacumab or the comparator (lomitapide) is likely to decrease these events. A lower number of events means an increased number of QALYs. This was done by using the LDL-C reduction data reported from clinical trials and estimating how much this reduced the cardiovascular events. The total QALYs and costs over the course of the average simulated lifetime were used to calculate the ICER. In the model, a discounted cost for evinacumab was used (reflecting the true cost to the NHS, should evinacumab be adopted). Costs for other drugs, including lomitapide, were based on the published list price of these drugs. Other considerations in the model included the cost to give evinacumab. Because it needs to be given as a drip (intravenous infusion), this costs money in terms of nursing time. There was also some monitoring costs for patient who take lomitapide including blood tests and liver scans that were accounted for. The negative impact of LDL-apheresis on quality of life was also input into the model.

<u>Accounting for uncertainty</u>

In any cost-effectiveness model, it is important to account for areas of uncertainty. This is because economic analysis is not an exact science, and the assumptions made and the values used in calculations can affect results. Key areas of uncertainty included:

- *The prognosis of HoFH and the baseline risk of cardiovascular events*. These arose because HoFH is a rare condition and its treatment is rapidly evolving, which has meant contemporary research into the condition is limited
- *Translating LDL-C levels to cardiovascular events (such as hearts attacks or strokes)*. Although it is widely accepted that LDL-C levels are directly related to the risk of cardiovascular events (28), there is uncertainty on the extent of this in HoFH. This is because most research has been conducted in the general population, but people with HoFH have much higher levels of LDL-C and reduction of this might not reduce cardiovascular events in the same way

- *The effectiveness of treatments for HoFH*. Whilst there was good trial evidence for evinacumab (22), this was not true for lomitapide which, due to the type of clinical trial that was conducted, can be viewed in the scientific field as lower quality data to support its use (13)
- *Costs and benefits*. There was considerable uncertainty regarding costs, for instance the dose of lomitapide required to have a significant clinical benefit, impacting the overall cost of the treatment. Additionally, any discounts that might be available to the NHS for lomitapide (which are not available publicly for commercial confidentiality) were not applied. Whilst there has been much research into quality of life in people who have had a cardiovascular event, this has not been conducted specifically in people with HoFH, who may experience different severity of events, impacting the overall level of benefit experienced by people with HoFH.

One way of testing or measuring the above uncertainty is to run something called sensitivity analyses, which means re-running the model with different assumptions or data inputs. In one-way sensitivity analyses, where one data input is changed at a time, the model was found to be most affected by assumptions about costs and age at the start of treatment.

3k) Innovation

Evinacumab is a highly innovative treatment for the following reasons:

- It is a "first in class drug", targeting a novel biochemical pathway. This means it works independently from other drugs used to treat HoFH and is fully effective when used with them. Naïve data suggests evinacumab is a highly effective drug available in the treatment of HoFH
- Evinacumab works in all people with HoFH, regardless of their genetic mutation type (see Section 2b)
- It can be used in most people with HoFH and can be used in adolescent populations (12 to 18 years inclusive). This is important as the earlier effective treatment to reduce LDL-C is tried, the better the long-term outcome for the patient
- Evinacumab is well-tolerated with a favourable safety profile.

These advantages of evinacumab, other than its effectiveness in lowering LDL-C, were not explicitly captured in the model, and all things being equal, should favour the use of evinacumab over lomitapide.

3l) Equalities

Equality concerns all people receiving fair access to treatment, regardless of who they are. In particular, this includes the 9 protected characteristics recognised in the UK (age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation) (30). Potential equality issues can relate directly to the disease

itself or through access to treatment. The following potential issues have been identified concerning HoFH and evinacumab:

- Some ethnic groups have a higher proportion of people who have HoFH, due to "founder effects" (when a new population is started from a bigger population, limiting genetic variation). This includes French Canadians, Afrikaners in South Africa, and Christian Lebanese (31)
- Evinacumab has a license for people ≥12 years, in contrast to lomitapide which is only allowed to be used in people 18 years and over (14). This leaves a significant unmet treatment need in this adolescent population which needs to be addressed. Age is a protected characteristic (30)

The availability of specialised care and access to LDL apheresis may be subject to geographical constraints within England and Wales. People from poorer socioeconomic backgrounds find access to care more difficult due to age-related, financial, and employment reasons (32). Socioeconomic status and regions lived in are not currently a protected characteristic, but nevertheless, equal access to healthcare provision in England is clearly desirable.

SECTION 4: Further information, glossary and references

4a) Further information

Further information on HoFH:

- NICE guideline CG71 Familial hypercholesterolaemia: identification and management (2008 updated 2019)
- NICE quality standards: Familial hypercholesterolaemia (2013) QS41
  British Heart foundation: Familial hypercholesterolaemia (information and support).
- NHS: High Cholesterol (information and advice)
- Heart UK: Homozygous familial hypercholesterolaemia (HoFH). (Information and signposting)

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Cardiovascular: relating to the circulatory system. Cardiovascular (CV) events refer to specific instances of disease or illness relating to the cardiovascular system (e.g. heart attacks or strokes). Cardiovascular disease (CVD) refers to disease caused by build-up of cholesterol plaques (atherosclerosis), causing CV events.

ANGPTL3: Angiopoietin-like protein 3

DBTP: double-blind treatment phase

HoFH: homozygous familial hypercholesterolaemia, a genetic condition where two genes relating cholesterol metabolism and/or uptake do not work correctly.

ICER: incremental cost-effectiveness ratio, a summary measure of how cost-effective an intervention is.

LDL-C: low density lipoprotein cholesterol, the “bad” cholesterol linked to CV events.

LDLR: low density lipoprotein receptor, a protein important for the uptake of cholesterol.

MHRA: Medicines and Healthcare products Regulatory Agency

NICE: National Institute for Health and Care Excellence

OLTP: open-label treatment phase

QALY: quality adjusted life-year, a measurement of effectiveness used in health economics.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Clarification questions

June 2023

File name	Version	Contains confidential information	Date
ID2704 evinacumab clarification questions to PM for company_ACiC_V1_06072023	1.0	Yes	06/07/2023
ID2704 evinacumab clarification questions to PM for company_V2_10072023_ACiC	2.0	Yes	10/07/2023
ID2704 evinacumab clarification questions to PM for	3.0	Yes	13/07/2023

company_V3withappendix_ 13072023_redacted			

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Treatment pathway

A1. Priority question. The EAG notes the updated European Atherosclerosis Society (EAS) guidelines published in May 2023(1) indicate that lomitapide and/or apheresis are both recommended as third-line treatments in patients eligible for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Please clarify the proposed positioning of evinacumab in the treatment pathway for adults including:

a) **whether it is intended that evinacumab would be used at the same point in the treatment pathway as lomitapide;**
b) **if apheresis (without lomitapide) is considered a comparator and if not, why apheresis is not deemed to be a relevant comparator;**
c) **whether evinacumab is intended to be used in patients not eligible for lomitapide or apheresis.**

The intended place in therapy for evinacumab is reported in sections B1.1 (Decision problem) and B1.3.6 (Patient management pathways) of the company submission. During development of the model and submission, the position of evinacumab in the treatment pathway was posited as third-line, at the same level as lomitapide, based on the then most up-to-date published guidance by the European Atherosclerosis Society (EAS) consensus guidelines of 2014 (2), UK HEART guidelines (3) and NHS England lomitapide commissioning guidance (4); this is illustrated in Figure 9 of the submission. In May 2023, shortly before the submission and model were completed, new EAS consensus guidelines were published (1) (Figure 8 of the submission). This clearly puts evinacumab as third-line treatment at the level as lomitapide, with the option of LDL apheresis to be used additionally to these drugs, but **NOT** instead of these drugs. Therefore, to answer the specific questions:

a) Yes. Evinacumab is intended to replace lomitapide at the same point in the pathway.
b) No. LDL apheresis is NOT considered a comparator in any scenario.

c) Evinacumab is indicated for use in all HoFH patient groups, as indicated by target LDL-C levels being achieved, regardless of other background treatments.

A2. Priority question. Please clarify the proposed positioning of evinacumab in the treatment pathway for adolescents.

Evinacumab is authorised for use in the adolescent population (12 to 17 years inclusive). Its position in the patient pathway for this population is the same as for adults, although it is noted that lomitapide is not a treatment option for this cohort. As with adults, evinacumab is indicated solely on the basis of whether target LDL-C levels have been achieved or not, independent of other background therapy.

ELIPSE trial baseline characteristics

A3. Priority question. The EAG notes that there is an imbalance between study arms (evinacumab and placebo) in the proportion of patients on lomitapide at baseline in ELIPSE, with a higher proportion on lomitapide in the evinacumab arm. Please provide an explanation for this discrepancy and the likely impact on the study results.

In the ELIPSE trial (5), there were 11 patients (25.6%) in the evinacumab arm and 3 patients (13.6%) in the placebo arm who received concomitant lomitapide (2:1 randomisation ratio). There was no significant difference between the expected and observed numbers of patients receiving lomitapide (p=0.267, using chi-squared test). Therefore there was no statistical imbalance and the distribution observed is due to chance, in line with randomisation. As lomitapide and evinacumab act independently of each other and do not exhibit synergy or antagonism, as evidenced by the ELIPSE trial (Section B.2.7.3 of submission, Table 17), it is not expected this distribution should impact on results.

A4. Priority question. The EAG notes that it is reported in the company submission that n=12 patients have low-density lipoprotein receptor (LDLR) negative/negative mutations.

a) **Please clarify the definition of negative/negative;**
b) **Please provide the number of patients with LDLR negative/negative at baseline for each study arm in ELIPSE.**

Information is provided in summary in the company submission report and fully described in the Clinical Study Report (CSR) provided to the EAG.

a) The definition of negative/negative, provided in Section B.2.3.1.3 and B.2.7.2 and consistent with what was used in ELIPSE, is defined as “Genotypically negative/negative - where mutations such as premature stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations (CNVs) are predicted to result in the loss of function of both LDLR alleles”, in line with the definition provided by Chora et al. (2018) (6). The exact loss in LDLR functionality is not defined in negative/negative patients.
b) In ELIPSE, [redacted] in the placebo arm and [redacted] in the treatment arm were classified as negative/negative, with [redacted] overall matching this description (Table 10, ELIPSE double-blind CSR). Note that this distribution does not indicate a statistical imbalance (p=0.138, chi squared test).

A5. Priority question. Please provide the number of patients in each trial arm for the following treatment combinations at baseline in ELIPSE:

a) **lomitapide and apheresis (irrespective of other lipid lowering therapy (LLT));**
b) **lomitapide without apheresis (irrespective of other LLT);**
c) **apheresis without lomitapide (irrespective of other LLT);**
d) **not on lomitapide or apheresis (irrespective of other LLT).**

[redacted]

6. Priority question. Please provide the proportion of patients with LDLR null-null or negative/negative who were also on lomitapide at baseline in ELIPSE for each treatment arm.

Evinacumab arm:

[redacted]

Placebo arm:

[redacted]

7. Please provide all the available baseline characteristics for each study arm for the following subgroups of patients in ELIPSE:

a) **patients not on lomitapide (n=51);**
b) **patients on lomitapide (n=14);**
c) **patients on apheresis (n=22);**
d) **patients not on apheresis (n=43);**
e) **patients not on lomitapide or apheresis.**

These data, all baseline characteristics stratified by background treatment (and multiple permutations of this), would require *de novo* analysis of individual patient data (IPD) which would be very time-consuming. The company questions the value of these data for the following reasons:

1. The mechanism of action of evinacumab (ANGPTL3 inhibition) is independent of all other forms of background or comparator treatment, including lomitapide, LDL apheresis, PCSK9 inhibitors, ezetimibe, and statins. Evinacumab neither exhibits synergy or antagonism when used with other forms of lipid lowering therapy (LLT).
2. The mechanistic independence of evinacumab has already been empirically confirmed by data from the ELIPSE trial (5), with no differences in the primary outcome reported in patients receiving or not receiving the principal background medications (Section B.2.7.3, Table 17 of submission).

3. The number counts for these subgroups are likely to be very low, and possibly zero in some cases. This will make it unfeasible to conduct any statistical analyses, and without this it is not clear what conclusions can be drawn. Additionally, as all available baseline characteristics are requested, this would result in a multitude of very large tables which would be challenging to interpret, even in a qualitative manner.
4. The use of these forms of background LLT were not predefined subgroups of interest in the scope (Table 1 of the company submission). Therefore, detailed analyses are out of scope.
5. ELIPSE was a phase 3 RCT adjudged to be of high quality and low risk of bias, which is a notable achievement in the field of HoFH. There is no indication that there were any issues with randomisation that would lead to imbalances in the characteristics of the patients receiving evinacumab or placebo. Therefore, all things considered, it would be expected that the distribution of baseline characteristics would be equal between groups.

For these reasons, the requested analysis has not been performed.

A8. Please provide a breakdown of the baseline lipid lowering therapies for the subgroup of patients LDLR null/null or negative/negative for each study arm in ELIPSE.

For null/null patients:

Evinacumab arm:

[redacted]

Placebo arm:

[redacted]

A9. Please provide a breakdown of the frequency of apheresis treatments used at baseline for each study arm in ELIPSE.

LDL apheresis was a stratification factor for randomisation in the ELIPSE trial (Table 7, CSR), so the proportion of patients receiving LDL apheresis was similar in each arm, with 14 patients in the evinacumab arm (32.6%) and 8 patients in the placebo arm (36.4%). Of these, the CSR reports

[redacted] The exact number of patients in each

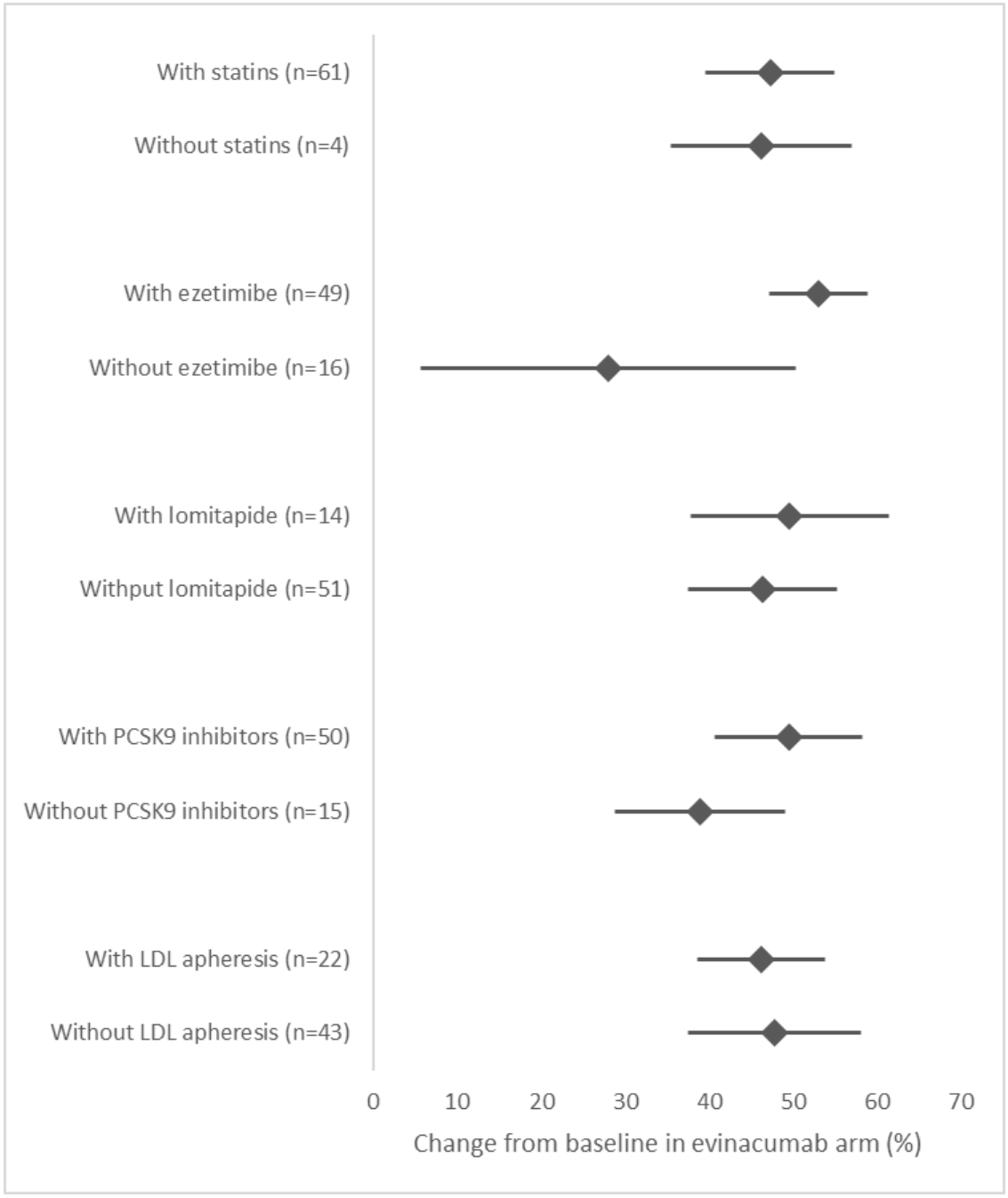
frequency group stratified by intervention arm was not reported in the CSR and would require *de novo* IPD analysis. We do not believe this would add value.

ELIPSE trial results

A10. Priority question. Please provide a forest plot for the subgroup results by background LLT presented in company submission Table 17 (Percent change in low-density lipoprotein cholesterol (LDL-C) from baseline to Week 24 by background LLT).

These data were reported in Table 17 of the company submission (Section B.2.7.3). These are presented as a Forest plot below.

Figure illustrating subgroup analyses conducted on background LLT.



A11. Priority question. Please provide:

a) **the number of patients in each treatment arm;**
b) **the results for the primary efficacy outcome (percent change in LDL-C from baseline to Week 24); and**
c) **the results for absolute reduction in LDL-C (mmol/L) from baseline to week 24;**

in ELIPSE for the following subgroups of patients:

a) **people who were on apheresis and not on lomitapide at baseline (irrespective of other LLT);**
b) **people who were on lomitapide and not on apheresis at baseline (irrespective of other LLT);**
c) **people who were on apheresis and lomitapide at baseline (irrespective of other LLT);**
d) **people who were not on apheresis or lomitapide at baseline (irrespective of other LLT).**

For question a) the number of patients in each treatment arm, please see response above to A5.
Please see the response to A7 for the rationale as to why analyses (b)(c) would be time-consuming and we believe would not add value to the decision problem (of which, they are out of scope). Published analyses are reported in Section B.2.7.4 of the submission and represented graphically in the response to A10.

A12. Priority question. Please provide the results for absolute reduction in LDL-C (mmol/L) from baseline to week 24 for each trial arm in ELIPSE for the following subgroups:

a) **all those reported in company submission Table 17;**
b) **patients with LDLR negative/negative at baseline;**
c) **patients with null/null <2% activity at baseline ;**
d) **patients with null/null <15% activity at baseline;**
e) **patients with null/null or negative/negative at baseline.**

Please see the response to A7 for the rationale as to why these analyses would be time-consuming and we believe would not add value to the decision problem. Panel B of Figure 20 in the submission reports on a waterfall plot of absolute LDL-C reduction stratified by individual mutation genotype.

The value of further analyses in the absolute reduction in LDL-C is questionable, especially when considered at an individual level (as would be implied by the analyses). Absolute reductions in LDL-C are dependent on many factors, most notable the baseline LDL-C level, which is variable between patients. In contrast, relative reductions in LDL-C are more consistent across populations and are independent of baseline LDL-C or other factors. It is noted that in all the pivotal trials of LLT we identified, relative reduction in LDL-C was used as the primary outcome (5, 7-9). The relative reduction in LDL-C has also been used as the effect of interest in all economic models we have identified in this disease area. ▌

A13. Please provide the results for least squares (LS) mean [± standard error (SE)] percent change in LDL-C from baseline to Week 24 for each trial arm in ELIPSE for the following subgroups:

a) **patients with LDLR negative/negative at baseline;**
b) **patients with null/null <2% activity at baseline;**
c) **patients with null/null <15% activity at baseline;**
d) **patients with null/null or negative/negative at baseline.**

*We feel that these analyses would be inappropriate given the small sample sizes involved, and would lead us to question the validity of results.*Other clinical trials for evinacumab*

A14. Please clarify if the Rosenson *et al.* 2020(10) study reported in company submission Section B.2.10.4 for adverse events included homozygous familial hypercholesterolemia patients and if so, why it was not discussed in the clinical efficacy sections of the company submission. Please provide any relevant clinical efficacy data from this study.

The study by Rosenson et al. (2020) (10) was in patients with refractory hypercholesterolaemia, with no participants with HoFH, so was out of scope for reporting efficacy data. However, given that it is to date the largest trial that has used evinacumab as an intervention, and given the relative paucity of data in this field, it was included as additional information to inform the safety of the drug. This was because it was considered most, if not all, adverse reactions due to evinacumab would be agnostic to the form of hypercholesterolaemia the drug was being used to treat.

Matching Adjusted Indirect Comparison (MAIC)

A15. Priority question. The EAG notes that for unanchored matching-adjusted indirect comparisons (MAICs), it is critical that attempts to adjust for all potential prognostic factors and treatment effect modifiers that are in imbalance between arms are made, as outlined in NICE decision support unit technical support document (DSU TSD)18(11). Given the difficulty in

confirming which factors are prognostic/effect modifying, the EAG considers it best practice to adjust for all baseline characteristics reported in the relevant studies.

a) **Please clarify whether the MAIC with lomitapide used to inform the company's base case and reported in company submission Section B.2.9.4.3 has been fully adjusted for all baseline characteristics reported in the relevant studies.**
b) **Please conduct a fully adjusted MAIC and ensure all reported baseline characteristics are balanced between the studies, if not already provided, for the comparison of the evinacumab arm from ELIPSE and lomitapide from Cuchel *et al.* 2013(8) and provide the following:**
    i) **the baseline characteristics after matching;**
    ii) **the results for LDL-C as provided in Table 21 of the company submission for percentage change in LDL-C from baseline;**
    iii) **the results for absolute reduction in LDL-C (mmol/L) from baseline to week 24.**
c) **Please comment on any factors that could not be adjusted for and the impact this lack of adjustment is expected to have on the results.**

The MAIC with lomitapide was challenging due to the low patient sample size of the pivotal lomitapide trial (n=29 in the intention-to-treat [ITT] group) (8) and the poor reporting of this trial. A full description of the methodology and rationale for the selection of the potential effect modifiers and prognostic factors is reported in Appendix D.2.4.2 of the submission, with age, baseline LDL-C, and history of coronary heart disease (CHD) being used as matching covariates.

However, it is worth noting at this point that matching was mainly limited by the reporting of aggregated baseline characteristics of the lomitapide pivotal trial (reported only in the supplementary material) (8). Apart from the factors already identified, it would only be possible to further match based on sex (gender); body mass index (BMI); method of diagnosis; ethnicity; and background drugs (of which statins and ezetimibe were used almost ubiquitously, and other older drugs such as fibrates hardly used at all, rendering this analysis of no value). It was simply not feasible to match with any more factors given the limited sample size of both Cuchel

et al. (2013) and the IPD from ELIPSE. The company consider that further MAIC analyses are not possible.

Additionally, for reasons discussed in response to A11, absolute reductions in LDL-C were never considered an informative outcome in the MAIC, and these analyses were not undertaken.

A16. Priority question. The EAG notes that in the company submission Section B.2.9.4.3 it is reported that for the MAIC, "the low [estimated sample sizes] in the cohort with lomitapide patients excluded meant meaningful analysis was not possible". The EAG acknowledges that there is therefore likely to be greater uncertainty in the results of this MAIC. However, the EAG considers that this comparison is important to accurately reflect the appropriate population in ELIPSE for a comparison with lomitapide. Therefore, for the MAIC conducted by the company for the comparison between evinacumab from ELIPSE excluding patients who have received lomitapide and lomitapide from Cuchel *et al*. 2013(8), please provide:

a) **the baseline characteristics after matching;**
b) **the results for LDL-C as provided in Table 21 of the company submission for percentage change in LDL-C from baseline;**
c) **the results for absolute reduction in LDL-C (mmol/L) from baseline to week 24.**

This analysis was undertaken by excluding the patients receiving lomitapide from the ELIPSE trial, but this had a large effect on the estimated sample size (ESS), reducing it to 3.9. In the opinion of the company, this negates any value this analysis can add and renders the data highly unstable (12). However, the relevant data is reported below. Note that as with the full MAIC, there was no significant difference between groups, and absolute reductions in LDL-C were not analysed.

Table reporting MAIC comparison of evinacumab with lomitapide with lomitapide patients removed from MAIC (reduction in LDL-C from baseline).

Method	Matching variables	Evinacumab N/ESS	Lomitapide N/ESS	Mean (95% CI) evinacumab	Mean (95% CI) lomitapide	Mean Difference (95% CI) evinacumab vs lomitapide
Unadjusted naïve ITC	NA	32.0	29.0	-46.42 (-57.62 to -35.23)	-40.1 (-51.47 to 28.73) [a]	6.32 (-9.63 to 22.27)
MAIC	Age, CHD, LDL-C	3.9	29.0	-33.83 (-96.84 to 29.17)	-40.1 (-51.47 to 28.73) [a]	-6.27 (-38.64 to 26.1)
MAIC (sensitivity analysis)	Age	16.7	29.0	-54.94 (-65.16 to -44.72)	-40.1 (-51.47 to 28.73) [a]	14.84 (-0.40 to 30.08)

Key: CHD, coronary heart disease; CI, confidence interval; ESS, effective sample size; ITC, indirect treatment comparison; LDL-C, low-density lipoprotein cholesterol; MAIC, matching-adjusted indirect comparison; N, number of patients; NA, not applicable.

Note: [a] Data presented to no decimal places because that is what is reported in Cuchel et al. 2013.

A17. Priority question. The EAG notes that there are two studies used to provide efficacy data for apheresis in the economic model (D'Erasmo *et al.* 2021(13) and Pottle *et al.* 2019(14)). Please provide a fully adjusted MAIC using the methods described in question A15 to ensure all reported baseline characteristics are balanced between the studies, for the comparison between the evinacumab arm from ELIPSE and apheresis. Please provide:

a) **justification for the study used to inform apheresis in the MAIC;**
b) **the baseline characteristics after matching;**
c) **the results for LDL-C as provided in Table 21 of the company submission for percentage change in LDL-C from baseline;**
d) **the results for absolute reduction in LDL-C (mmol/L) from baseline to week 24.**

As background, the systematic literature review (SLR) performed on interventions for the treatment of HoFH revealed that research into the efficacy of LDL apheresis is particularly limited, with no experimental trials identified. Instead, research is mainly limited to retrospective analyses of disease registries which are subject to considerable levels of confounding and bias. Issues identified included different

apheresis technologies used; different historical timeframes (and therefore different background LLT); different measurements of the primary outcome and poor reporting of this (acute reductions, long-term reduction, median interval reductions); small sample sizes; lack of comparative data; and overall poor reporting (including of baseline characteristics). Against this backdrop, the company was unable to identify robust evidence on the efficacy of LDL apheresis in this population. After some consideration the data reported in the study by D'Erasmo et al. (2021) was considered to be the most reliable (13), based on its large sample size and adequate description of the outcome measure reported. The results from this study were also consistent with feedback from KoLs, who confirmed that mean interval reduction of around -40% is expected from LDL apheresis.

Due to the reasons discussed above, it was not possible to include LDL apheresis in the MAIC. All identified studies were excluded on the basis of sample size or methodology (discussed in Appendix D.2.2.5).

Additionally, the value of performing a MAIC with LDL apheresis data is highly questionable, as this technology was categorically NOT considered a comparator in the decision problem (see response to A1 and relevant sections in the submission for the rationale for this).

A18. Priority question. For the MAIC with lomitapide used to inform the company's base case and reported in company submission Section B.2.9.4.3, please provide the following:

a) **the baseline characteristics after matching;**
b) **results for absolute reduction in LDL-C (mmol/L) from baseline to week 24 from the fully adjusted MAIC in the company submission for the comparison of evinacumab from ELIPSE versus lomitapide from Cuchel *et al*. 2013(8).**

The ELIPSE baseline characteristic were matched for age, CHD status, and baseline LDL-C in the MAIC.

a) Baseline characteristics were not reported in the original MAIC because this was not considered useful data; ELIPSE was a randomised trial and the baseline characteristics were evenly distributed between arms. To report other baseline

characteristics of the matched patients from the ELIPSE study in the MAIC would require de novo analysis which would be difficult and time-consuming to implement.

b) Absolute reductions in LDL-C in the ITT group were not reported by Cuchel et al (2013), so this analysis is not feasible. Whilst it may be possible to estimate these data through calculation, it would not be logical to do this. This is because the only way we can match/compare the efficacy of lomitapide and evinacumab is through their relative efficacy, not the absolute effect of the drugs on LDL-C, as this is dependent on baseline LDL-C, which differ between trials and between individuals. Baseline LDL-C was one of the matching factors in the ITC, so has been accounted for already in the MAIC (see also response to A12).

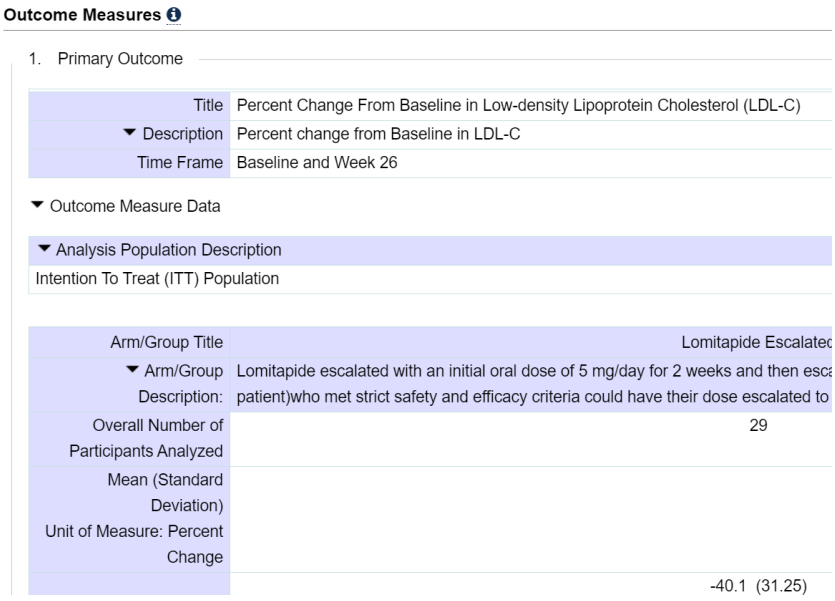
A19. Priority question. Please provide the baseline characteristics after matching for the MAIC in the company submission for the comparison of evinacumab from ELIPSE versus lomitapide from Cuchel *et al*. 2013(8).

The EAG has confirmed that this question is a repetition of question A18a above.

Statistical methods

A20.Priority question. Please can the company clarify the reference source used to obtain intention to treat (ITT) data for lomitapide from Cuchel *et al.* 2013(8) that is used in the MAIC with lomitapide used to inform the company's base case and reported in company submission Section B.2.9.4.

The reference for the ITT results from the Cuchel et al. (2013) trial was stated in the submission, and was taken from the ClinicalTrials.gov protocol, with published results in the relevant results tab (NCT00730236). A screenshot is provided below. This data also matches the longitudinal graph reported in the study.



Outcome Measures

1. Primary Outcome

Title	Percent Change From Baseline in Low-density Lipoprotein Cholesterol (LDL-C)
Description	Percent change from Baseline in LDL-C
Time Frame	Baseline and Week 26

Outcome Measure Data

Analysis Population Description
Intention To Treat (ITT) Population

Arm/Group Title	Lomitapide Escalated
Arm/Group Description:	Lomitapide escalated with an initial oral dose of 5 mg/day for 2 weeks and then esca patient)who met strict safety and efficacy criteria could have their dose escalated to
Overall Number of Participants Analyzed	29
Mean (Standard Deviation) Unit of Measure: Percent Change	
	-40.1 (31.25)

21. Please explain how the covariates used in the mixed-effects (MMRM) model to estimate change in LDL from baseline in ELIPSE were selected for inclusion.

The covariates used in the mixed model (MMRM) was pre-specified in the protocol and the Statistical Analysis Plan. The model included the fixed categorical effects of treatment group (evinacumab versus placebo), randomization strata (apheresis [Yes/No] and region [Japan, Rest of World]), time point (weeks 2, 4, 8, 12, 16, 20, and 24), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction.

Justification of inclusion of covariates:

Stratification was used in the study to ensure balance of treatments across the covariates apheresis [Yes/No] and region [Japan, Rest of World], therefore these were included as covariates in the model (See European Medicines Agency, Guideline on adjustment for baseline covariates in clinical trials). The baseline LDL-C which is correlated with LDL-C outcome was also included in the model to improve the efficiency of the mixed model. The time point was included in the model to account for repeated collection of data in the study. Interaction terms were included

to assess if changes of the outcome of LDL-C differ over time within the categories of these groups.

A22. Please clarify if the results presented in company submission Table 17 (Percent change in LDL-C from baseline to Week 24 by background LLT) were calculated using the same methods used for the primary efficacy outcome assessment in ELIPSE including the use of a mixed-effects model for repeated measures.

The results presented in company submission Table 17 (Percent change in LDL-C from baseline to Week 24 by background LLT) were not calculated using the same methods used for the primary outcome assessment in ELIPSE (mixed-effects model for repeated measures). The results provided in Table 17 (see below) were descriptive summaries.

Table 17. Percent change in LDL-C from baseline to Week 24 by background LLT.

Background therapy at baseline, mean (SD)*	**Background therapy at baseline**		**No background therapy at baseline**	
	Placebo IV Q4W	**Evinacumab 15 mg/kg IV Q4W**	**Placebo IV Q4W**	**Evinacumab 15 mg/kg IV Q4W**
Statin	n=61		n=4	
	2.2 (32.3)	-47.3 (30.6)	-5.7 (22.7)	-46.2 (11.0)
Ezetimibe	n=49		n=16	
	-2.0 (30.6)	-53.1 (21.0)	12.2 (34.1)	-28.0 (45.5)
Lomitapide	n=14		n=51	
	-17.2 (47.6)	-49.6 (22.5)	4.5 (28.4)	-46.4 (32.3)

PCSK9 inhibitor	n=50		n=15	
	1.7 (30.3)	-49.5 (31.9)	0.7 (36.2)	-38.9 (20.1)
Lipoprotein apheresis	n=22		n=43	
	-7.3 (34.3)	-46.2 (18.1)	6.8 (29.2)	-47.8 (34.4)

Abbreviations: IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, once every 4 weeks; SD, standard deviation.

* Patients taking these medications with or without other medications.

Data from Raal et al. (2020)

Section B: Clarification on cost-effectiveness data

Population

B1. Priority question: The EAG considers that given most patients in ELIPSE had a history of cardiovascular disease (CVD), it is crucial the model considers the distinction between primary prevention patients (those without a history of cardiovascular (CV) events) and secondary prevention patients (those with a history of CV events) at baseline, as was also done in technology appraisal (TA)694(15), among other previous TAs.

Please include in the company's base case a proportion of secondary prevention patients at baseline, in addition to the already considered primary

prevention patients. If the company does not include this in their base case, please conduct this as a scenario analysis.

In order to undertake this analysis, please:

a) **Distribute the secondary and primary prevention patients at baseline according to the baseline distribution of history of CVD in ELIPSE;**
b) **Distribute the secondary prevention patients across the post-CV event health states, taking into account the utilities and costs associated with the post-CV health states;**
c) **Consider the difference in costs of secondary prevention patient CV events as outlined in question B418.**
d) **Consider the utility difference in experiencing multiple CV events as outlined in question B21.**
e) **Consider the permanent increase in risk of current events as outlined in B8**
f) **Consider the difference in risk of CV mortality caused by non-fatal CV events as outlined in B9**

a) and b) For the purpose of informing the baseline distribution across the cost-effectiveness model health states, the data available on the history of CV events for the ELIPSE trial cohort is limited. The proportion of the cohort with any CV event history or risk factors was 92.2%. The proportion having previously had an acute MI was 18.8% and having a history or angina (chronic or stable) was 31.3%. We do not have access to data on the history of cerebrovascular events in these patients.

The model does not contain health states that differentiate between a single or multiple event history. Therefore, patients having had an MI can move to stroke states, and vice versa. On the basis, for the purpose of this scenario, we evenly divide the proportion with a history of MI between the post-stroke and post-MI health states. We then conservatively assume that proportion with a history of angina can be added whilst ignoring that some will also have a history of an MI or stroke. These patients were evenly distributed between the post-stable angina and post-unstable angina health states. The baseline distribution of patients across the model health states at baseline is shown in Table B1.1.

Table B1.1. Baseline distribution of patients across the model health states at baseline

Health state	**Baseline distribution (%)**
Stable HoFH	50.0%
Stable angina	0%
Unstable angina	0%
MI	0%
TIA	0%
Stroke	0%
Post-Stable angina	15.6%
Post-Unstable angina	15.6%
Post-MI	9.4%
Post-TIA	0%
Post-Stroke	9.4%
CV-death	0%
General death	0%
Dead	0%

Table B1.2. Economic model outputs for chosen scenarios

Scenario	Evinacumab versus lomitapide		
	Incremental costs	Incremental QALYs	NMB*
Base-case	[redacted]	[redacted]	[redacted]
Scenario B1.1	[redacted]	[redacted]	[redacted]

*cost-effectiveness threshold = £30,000 per QALY gained

The results obtained when using the baseline distribution given in Table B1.1 are shown in Table B1.2.

c) The model has continued to use the combined cost data obtained from Danese et al. (2016), therefore, no changes have been included in developing this scenario.

d) Due to the absence of health states to represent patients having had multiple CV events, we are unable to include the suggested change in this scenario.

e) As described in the response to question B8 below, the requested scenario analysis describes the current model base-case settings. Therefore, there are no changes required to include this within the current scenario.

f) The results presented in Table B1.3 combine the changes to the model inputs described in part B1 a) and B9.

Table B1.3. Economic model outputs for additional scenario analyses

Scenario	Evinacumab versus lomitapide		
	Incremental costs	Incremental QALYs	NMB*
Base-case	[redacted]	[redacted]	[redacted]
Scenario B1.1 + B9.1	[redacted]	[redacted]	[redacted]
Scenario B1.1 + B9.2	[redacted]	[redacted]	[redacted]
Scenario B1.1 + B9.3	[redacted]	[redacted]	[redacted]
Scenario B1.1 + B9.4	[redacted]	[redacted]	[redacted]

*cost-effectiveness threshold = £30,000 per QALY gained

Model structure

B2. Priority question: Please explain why the model only allows for patients to transition to the transient ischaemic attack (TIA) from the stable homozygous familial hypercholesteraemia (HoFH) health state and not from other event health states?

The model has adopted a relatively simple representation of the natural history of cardiovascular disease. It was considered that a more realistic health state structure would not be advantageous, given the absence of evidence from a HoFH population from which to derive inputs. As such, the model does not contain health states for patients having experienced multiple events (e.g., patients with unstable angina also having had a stroke). Although this represents a limitation, there are precedents for this structure (e.g., NICE TA385).

In the absence of tracking of patients' event history, there is the potential that the state healthcare costs may decrease, or state utility may increase when patients transition to a less severe event state. This would occur, for example, for a transition from post-stroke to TIA followed by post-TIA, which would imply an apparent

increase in utility from 0.628 to 0.760. To prevent such illogical transitions, only those transitions that imply progression to a more severely impacted health state (utilities and healthcare costs) are possible.

B3. Priority question: Please explain why the model only allows for patients to transition to the stable angina health state from the stable HoFH health state and not from other event health states?

The reason for this restriction follows the same reasoning as the response to question B2. The cost-effectiveness model does not contain health states for multiple events, as such the possible transitions are restricted to those that lead to a worsening of the condition in terms of quality of life and healthcare costs.

B4. Priority question: In addition to the health states outlined in the economic model, opinions provided by the EAG's independent clinical experts noted that acute coronary syndrome and revascularisation would also be CV events of interest (which were also included in TA694(15)).

a) **Please explain why these were not considered in the model given the requirement for revascularisation was included as an outcome in the final scope?**
b) **As a scenario, please include both these CV events in the model.**

For revascularisation, it has been assumed that where this is urgent and undertaken following an event, such as MI or unstable angina, that its impacts are captured within the cost and utility data for those health states. The model has not captured those procedures that may be elective, and whose occurrence is not associated with a cardiac event represented in the economic model. This is a limitation of the economic model, however, the impact of this omission is expected to be small and biased against the treatment that provides the greater reduction in LDL-C concentration. With respect to the omission of elective revascularisation, therefore, any estimates of the cost-effectiveness of evinacumab versus lomitapide can be considered conservative.

For acute coronary syndrome, which encompasses events such as unstable angina and MI, we consider that this event is captured by the cardiac events represented within the economic model.

CV risk

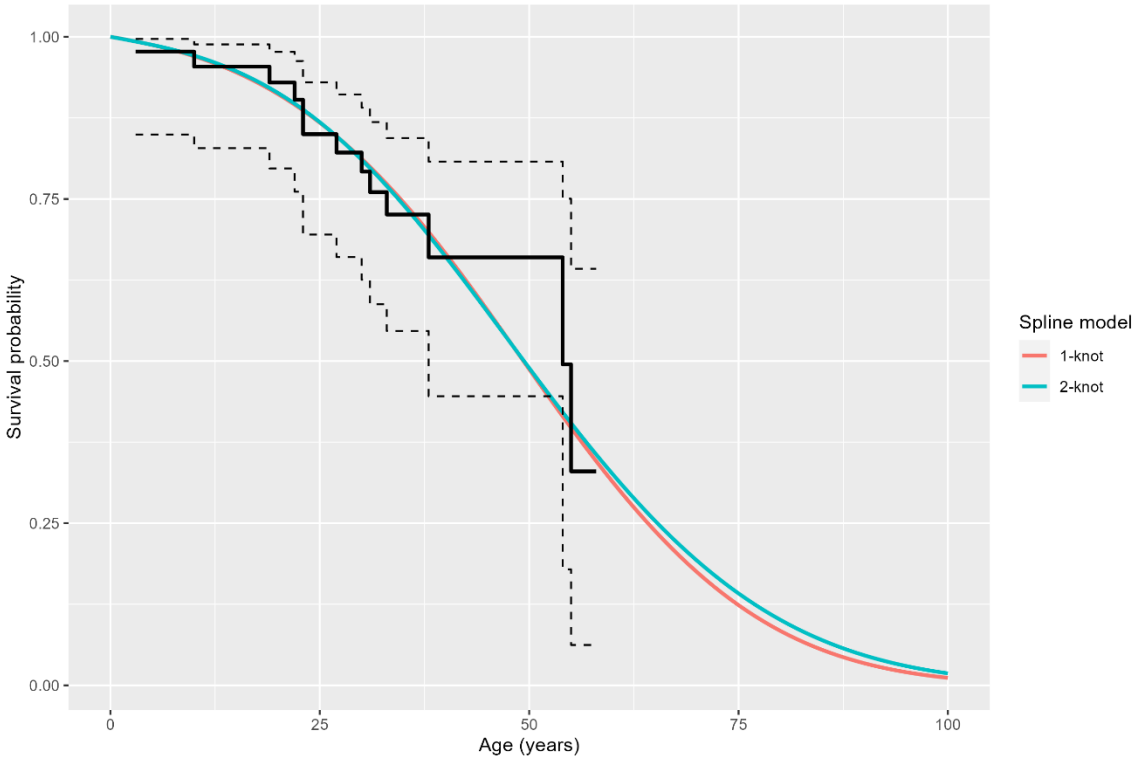
B5. Priority question: The company outlines in the CS that spline models were considered but ultimately rejected as they did not lead to a significant improvement in fit. Please provide the one and two knot spline models estimated as options to model CVM in the excel model.

The results for 1-knot and 2-knot spline models, obtained in R using the flexsurvspline function of the flexsurv package, are given in the table below (Table B5.1). The figure below shows the survival curves obtained using these spline-based models, along with the Kaplan-Meier survival curve estimate.

Table B5.1 Results for 1-knot and 2-knot spline models

Output	Model [mean, (SE)]	
	1-knot spline	**2-knot spline**
AIC	145.62	150.97
BIC	147.60	154.73
Gamma0	-6.156 (2.346)	-6.08 (2.325)
Gamma1	1.106 (0.871)	1.05 (0.913)
Gamma2	-0.618 (0.563)	-0.299 (1.94)
Gamma3	NA	0.027 (4.222)

Figure B5.1 survival curves obtained using spline-based models



B6. Priority question: The company has estimated the number of non-fatal CV events from the number of fatal CV events identified in Thompson *et al.* 2015(16) using a fatal to non-fatal CV events ratio from Ward *et al.* 2007(17) (K215:219 of the clinical data tab of the economic model). As the company explains in the company submission, this ratio is based on general population UK register data and is not specific to HoFH populations. The EAG's clinical experts considered that a ratio derived from the general population was unlikely to be reflective of the HoFH population as this could be higher or lower than the general population. Therefore, please conduct two scenarios, one where the impact of increasing the ratios is explored, and an additional scenario where the impact of decreasing the ratios is explored.

The age group specific ratios of the incidence of non-fatal to fatal cardiovascular events, obtained from Ward et al., have been varied as shown in Table B6.1. The lower (upper) scenario is obtained by decreasing (increasing) the base-case value by 50%. The incremental costs and QALYs for these scenarios, along with their base-case values, are presented in Table B6.2.

Table B6.1. Scenarios varying ratio of non-fatal to fatal event incidence

Age group	Non-fatal to fatal events incidence ratio		
	Base-case	Scenario B6.1 (base-case*0.5)	Scenario B6.2 (base-case*1.5)
40-54	9.2	4.6	13.8
55-65	7.1	3.5	10.6
65-74	5.1	2.5	7.6
75-84	5.8	2.9	8.7
85-100	6.1	3.0	9.1

Table B6.2. Economic model outputs for chosen scenarios

Scenario	Evinacumab versus lomitapide			
	Incremental costs	Incremental QALYs	NMB*	ICER
Base-case	[redacted]	[redacted]	[redacted]	Dominant
Scenario B6.1	[redacted]	[redacted]	[redacted]	Dominant
Scenario B6.2	[redacted]	[redacted]	[redacted]	Dominant

*cost-effectiveness threshold = £30,000 per QALY gained

The results for this scenario analysis, given in Table B6.2, show the net monetary benefit to vary between £2.6 million and £3.4 million when the ratios of the incidence of non-fatal to fatal cardiovascular events are simultaneously varied according to the ranges in Table B6.1.

B7. Priority question: The company used Ward *et al. 2007(17)* to inform the distribution of events which made up the non-fatal CV events, namely; stable angina, unstable angina, Myocardial Infarction (MI, transient ischemic attack (TIA) and stroke. The distributions assumed were informed using general population register data. The EAG's clinical experts considered that compared to general population estimates, cardiac related events (stable angina, unstable angina, MI) would be more frequent in HoFH populations compared with cerebrovascular events (TIA, stroke). As such, please provide a scenario

exploring an increase in the assumed distribution of non-fatal cardiac events with respect to cerebrovascular events for the HoFH modelled population.

We have performed a scenario analysis in which a greater proportion of CV events are cardiac events. This has been achieved by arbitrarily increasing the proportions for stable angina, unstable angina and MI by 20%. The proportions for cerebrovascular events were then down weighted by the appropriate factors to ensure that each row sums to 100%. The proportions for CV death were left unchanged. The set of model inputs used in this scenario analysis are presented in Table B7.1, which is based on Table 33 of the company submission.

Table B7.1. Revised model inputs for scenario in which cardiac events are relatively more frequent

Age group (sex)	Stable angina	Unstable angina	MI	TIA	Stroke	CVD death
40-54 (male)	37%	13%	35%	2%	3%	10%
55-65 (male)	39%	9%	21%	5%	13%	13%
65-74 (male)	26%	10%	21%	7%	20%	16%
75-84 (male)	23%	10%	19%	6%	27%	14%
85-100 (male)	26%	12%	22%	1%	26%	14%
40-54 (female)	39%	14%	10%	12%	17%	9%
55-65 (female)	42%	9%	11%	7%	21%	11%
65-74 (female)	24%	6%	15%	6%	32%	17%
75-84 (female)	18%	4%	12%	9%	42%	15%
85-100 (female)	16%	3%	12%	8%	46%	15%

The headline model results for the current base-case and the scenario using adjusted event proportions are given in Table B7.2.

Table B7.2. Economic model outputs for chosen scenarios

Scenario	Evinacumab versus lomitapide			
	Incremental costs	Incremental QALYs	NMB*	ICER
Base-case	[redacted]	[redacted]	[redacted]	Dominant
Scenario B7.1	[redacted]	[redacted]	[redacted]	Dominant

*cost-effectiveness threshold = £30,000 per QALY gained

B8. Priority question: Please conduct a scenario in which after a CV event, the relative risk of a subsequent (but same type) of event is permanently increased for the patient's lifetime, and remains at 1.5 (and not 1.2) for that specific event.

The requested scenario analysis describes the current model base-case settings. As described in Section B.3.3.4.1 of the CS: "In line with NICE TA694 and TA393 (158, 178), this economic model applies a 1.5 fold increase in the baseline hazards of CV death in all post-event health states. The same increase was applied to the risk of non-fatal cardiac events (SA, UA, MI) due to previous non-fatal cardiac events, and to the risk of non-fatal cerebrovascular events (TIA, IS) due to previous non-fatal cerebrovascular events."

Therefore, following an event (whether cardiac or cerebrovascular), the risk of the same event occurring is currently permanently increased by a factor of 1.5. Since this request corresponds to the model base-case, no further analyses have been performed in response to this request.

B9. Priority question: Opinion provided by the EAG's clinical experts is that not all CV events will lead to the same increase in relative risk of CV mortality (CVM) (cell E172 in the 'clinical data' tab of the economic model). Please conduct a scenario using increased relative risk of CVM values specific to each non-fatal CV event.

The model implementation is such that a change in risk following an event can only be implemented on the basis of prior cardiac or cerebrovascular event, rather than for each specific event (e.g., unstable angina). The current model base-case uses a multiplier of 1.5 for the risk of mortality following either a cardiac or cerebrovascular event. To address this request, we have performed scenario analyses in which the mortality risk multipliers differ according to whether the event was cardiac or cerebrovascular. The scenarios that were included are shown in table B9.1.

Table B9.1. Mortality multipliers used in the model base-case and additional scenario analyses

Scenario	Mortality multiplier	
	Cardiac event	Cerebrovascular event
Base-case	1.5	1.5
Scenario B9.1	1	1.5
Scenario B9.2	2	1.5
Scenario B9.3	1.5	1
Scenario B9.4	1.5	2

The model outputs for these scenarios are given in Table B9.2.

Table B9.2. Economic model outputs for mortality multiplier scenarios

Scenario	Evinacumab versus lomitapide			
	Incremental costs	Incremental QALYs	NMB*	**ICER**
Base-case	[redacted]	[redacted]	[redacted]	Dominant
Scenario B9.1	[redacted]	[redacted]	[redacted]	Dominant
Scenario B9.2	[redacted]	[redacted]	[redacted]	Dominant
Scenario B9.3	[redacted]	[redacted]	[redacted]	Dominant
Scenario B9.4	[redacted]	[redacted]	[redacted]	Dominant

*cost-effectiveness threshold = £30,000 per QALY gained

B10. Please conduct a scenario where the risk of CV death in the general population has been subtracted from the all-cause mortality applied in the model.

We were unable to provide the results of this scenario analysis. The reasons for this include i) the expectation that removing the general population risk of CV death from the risk of death from all causes will have a negligible impact on the modelled incremental outputs, ii) that age-specific data on death from all CV causes were not easily identified.

B11. In the company submission the company states that the use of the QRISK3 algorithm was explored, however the results were not included.

Additionally the algorithm has been included in the model but has been switched off. Please provide a scenario in which the CVD risk can be calculated using the QRISK3 algorithm in the model.

It is our view that there is, at best, no value in using the QRISK3 to predict baseline risk in an HoFH patient population, and at worst this may be misleading. Therefore, we have chosen not to present any analysis in which the baseline risk is informed in this way. The levels of LDL-C observed in HoFH patients are typically well above the range of those used in the development of risk prediction algorithms, such as QRISK3. These algorithms cannot be relied upon to produce credible predictions so far outside the sample from which they were constructed. The company has previously confirmed this with clinical specialists and economists familiar with this field of medicine.

It is likely that the QRISK3 would greatly underestimate the level of CV risk experienced by patients with HoFH. NICE outlines in one of its Clinical Knowledge Summaries (CKS) regarding CVD risk assessment and management, stating explicitly that QRISK assessment tool should not be used in people who are at high risk of developing CVD, including people with FH (18, 19).

Comparators and treatment efficacy

B12. Priority question. Please can the company justify using the Thompson imputed baseline LDL-C values in the company's base case instead of using the baseline LDL-C measured in ELIPSE.

We do not observe the outcomes of interest (those directly leading to mortality, quality of life impacts or health care resource utilisation), such as the frequency of CV events and mortality, in the clinical trials of the relevant treatments. Furthermore, there is not an established method of predicting the baseline risk of CV events based on LDL-C concentrations in a patient group as severe as HoFH. The use of QRISK3 was considered but deemed to be wholly unsuitable for this patient group (see response to B11).

The Thompson et al. study was one of very few sources from which the baseline risk of CV death could be estimated for an HoFH patient cohort. Furthermore, it has the

advantage of being a study from a UK centre. The baseline risk derived from these data represent the risk corresponding to the LDL-C concentrations in the Thompson et al. study cohort and not the ELIPSE trial cohort. Therefore, the cost-effectiveness model effectively models the effects of treatments in this patient cohort – after adjusting for differences with ELIPSE in the background treatments being received.

B13. Priority question: Given the considerable uncertainty in estimating the relative treatment effect between evinacumab and lomitapide through the MAIC and the lack of robust data to undertake a more appropriate analysis, please conduct a cost minimisation analysis, assuming that evinacumab and lomitapide have equal effectiveness.

We have performed a scenario analysis assuming that evinacumab and lomitapide have equal efficacy. An arbitrary shared efficacy of a 50% reduction in LDL-C concentration was chosen, a value that lies between those currently used in the economic evaluation base-case. A summary of the results for costs presenting both the base-case along with the scenario assuming equal efficacy is given in Table B13.1.

The results demonstrate that when equal efficacy is assumed, the cost savings associated with evinacumab compared to lomitapide increase. However, we would like to emphasise that a cost-effectiveness analysis is the most appropriate form of analysis in this circumstance in order to include the health gains associated with evinacumab compared to lomitapide.

Table B13.1. Summary cost outputs for base-case and scenario assuming equal efficacy

Outcomes	Technology		Incremental
	Evinacumab + SoC	**Lomitapide + SoC**	
Base-case cost results			
Drug costs	[redacted]	[redacted]	[redacted]
Monitoring costs	1,875	1,829	46
Health state costs	14,119	14,198	-79
CV death costs	-2,801	-2,914	113
Total costs	[redacted]	[redacted]	[redacted]
Cost results assuming equal efficacy			
Drug costs	[redacted]	[redacted]	[redacted]
Monitoring costs	1,860	1,860	0
Health state costs	14,145	14,145	0
CV death costs	-2,837	-2,837	0
Total costs	[redacted]	[redacted]	[redacted]

Abbreviations: CV, cardiovascular; QALYs, quality-adjusted life years; SoC, standard of care.

B14. Priority question. Please justify the approach of calculating LDL-C reductions associated with background treatments through the subtraction and addition of specific proportions of background treatments, when the estimates of efficacy coming from the MAIC already included the indirect underlying background treatment effects (Table 36). As such, please remove the step of subtracting and adding the effectiveness of background treatments from the model.

Our view is that the efficacy of treatments, in terms of relative change in LDL-C concentration, whether taken directly from the trial results or via the MAIC, should be considered independent of background treatments received. This assumption is based on the approach to the statistical analysis of the ELIPSE trial, which used the log scale to analyse the treatment effects. A scale on which the treatment effects

may be modelled as additive is typically sought for efficiency and for ease of interpretation of the results. The statistical analysis also did not include any treatment effect interactions, such as with background treatment or baseline LDL-C, which would be required if the efficacy were conditional on these covariates. Therefore, we conclude that it is reasonable to assume that the estimates of treatment efficacy used are independent of background treatment and LDL-C concentration.

Furthermore, we consider that it would be inappropriate not to adjust for background treatment differences. This is done in order that the baseline risk profile and LDL-C concentration (obtained from the Thompson et al. study) is more representative of the treatment mix observed in the ELIPSE study (considered more likely to represent current practice). For these reasons, we have not included this change in the updated the model base-case provided.

The likely impact of not adjusting for the background treatment mix differences is a higher LDL-C concentration at the point at which patients are eligible for evinacumab or lomitapide, therefore increasing the absolute reductions. This would then be expected to be favourable to evinacumab, being the treatment leading to the greatest relative reduction in LDL-C concentration.

For the following questions B15-17:

a) **When applying the treatment effectiveness measures in the model, please do not use the subtracting and adding of the effectiveness of background treatments method, as mentioned in B14**
b) **Please apply the reductions in LDL-C to the baseline LDL-C reported in ELIPSE.**

B15. Please evaluate the cost effectiveness of evinacumab against lomitapide using the results of the MAIC analysis requested in question A18.

In question A18, the EAG has requested that the MAIC be used to obtain an absolute reduction in LDL-C concentration from baseline to week 24. As described in the response to question A18, this is not considered feasible given the limitations in the data that are available across the relevant studies. Furthermore, the key assumption generally made that treatments have a consistent effect (across patients

and studies) in terms of the relative reduction in LDL-C concentration, implies that this would not be consistent on the absolute scale. Therefore, it would be inappropriate to derive an absolute reduction and then to apply this to the patient cohort in the cost-effectiveness model, without adjusting for differences in baseline concentrations.

B16. Please evaluate the cost effectiveness of evinacumab against placebo using the primary results from the ELIPSE trial.

This analysis would not reflect the intended positioning of evinacumab or the NICE decision problem, which is as an alternative to lomitapide. Therefore, we have not provided the requested results.

B17. Please evaluate the cost effectiveness of evinacumab against apheresis using the results of the MAIC analysis requested in question A17.

a) **Please conduct a cost minimisation analysis, assuming that evinacumab and apheresis have equal effectiveness.**

A comparison between evinacumab and apheresis would be outside the scope of the current appraisal and not relevant to the estimation of the cost-effectiveness of evinacumab versus lomitapide. Therefore, we have not conducted this analysis.

Furthermore, as described in the response to A17, it was found not to be possible to include LDL apheresis within a MAIC since all identified studies were excluded on the basis of sample size or methodology. Regarding the cost-effectiveness of evinacumab versus lomitapide, it is not anticipated that the results will be sensitive to magnitude of the efficacy of apheresis.

Health-related quality of life

B18. Priority question: The utility value for the stable HoFH health state is based on age and sex adjusted general population values. Please justify this

assumption and provide a scenario using mean EQ-5D data from ELIPSE for patients who have stable HoFH.

Changes in EQ-5D in HoFH are as a result of CV events, not the condition per se. To be consistent, we used utility values for health states from the general population who have had CV events (the only available data), consistent with other HTAs. A proportion of people (about 50%) in ELIPSE had already had an event at baseline, and we do not want to double count this in the model. ELIPSE was a double-blinded trial, so any benefits from evinacumab in terms of reduction in anxiety will be masked.

B19. Priority question: Please clarify why model 1 (general population) instead of model 2 (individuals with no history of CVD) from Ara & Brazier 2010(20) was used for the age-adjustment for published utility values (tab 'Model settings', cells E108:117). Please note that model 2 was used in TA393 and TA694.

a) **Please provide a scenario using model 2 (individuals with no history of CVD) from Ara & Brazier 2010 for the age adjustment for published utility values. Using model 2 will result in age- and sex- adjusted utility multipliers similar to those used in TA393(21) and TA694(15).**
b) **The EAG's clinical experts advised that HoFH patients experience CVD events at a much younger age, but the impact on health-related quality of life (HRQoL) is the same as other patients who experience the same event at an older age. As such, please provide a scenario where the age adjustment for the utility multipliers (tab 'Model settings', cells E108:117) is removed.**

Regression equation for individuals reporting no history of CVD (model 2) was deemed to be inappropriate considering a proportion of HoFH patients would have experienced CVD from an early age.

a) In TA694, EAG has questioned the use of model 2 (given it was derived from a population with no history of CVD) in subpopulation groups when statins are contraindicated or not tolerated and ezetimibe does not appropriately control LDL-C, or when maximally tolerated statin dose with ezetimibe does not

appropriately control LDL-C. For HoFH, the majority of patients would be treated with maximally tolerated statin plus other LLTs in order to adequately control LDL-C, thus model 2 was not suitable for estimating baseline utility for patients with HoFH.

b) A scenario in which the age adjustment multipliers were removed from tab 'Model settings', cells E108:117 has been added, and the results reflecting this scenario are given in Table B19.1.

Table B19.1. Results of removing age adjustment multipliers for utility values

	Total			**Incremental**				
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	INMB (£)
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	5,976,577	12.84	8.67	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

B20. Priority question: In the economic model, the utility value for MI was based on the angina utility value from Ara & Brazier 2010(20), but the post-MI utility reflects the post-heart attack utility value from the same publication. The EAG notes that a heart attack utility (0.721) is available from Ara & Brazier 2010(20).

a) Please explain why the heart attack utility (0.721) from Ara & Brazier 2010 was not used for the MI health state in the economic analysis?

In Ara & Brazier 2010, the sample size of patients experiencing an MI was small (N=31), thus stable angina utility value (N=271) was used in the economic analysis.

b) **Please provide a scenario analysis where the heart attack utility (0.721) from Ara & Brazier 2010(20) is used for the MI health state.**

A scenario in which the utility value for MI is 0.721 has been added, and the results reflecting this scenario are given in Table B20.1. The results demonstrate that the results of the analysis are robust to the utility estimate for MI.

Table B20.1. Results of using EAG preferred utility value for MI health state

	Total			**Incremental**				
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	INMB (£)
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	5,976,577	12.84	10.01	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

B21. Priority question: The EAG notes that in Ara & Brazier 2010(20), utility values are available for multiple CV events (angina+other CV event, heart attack+other CV event, stroke+other CV event) as well as related post event utilities.

a) **The EAG's clinical experts advised that experiencing multiple CV events will have a greater impact on patient HRQoL than a single event. Please justify why utility values for multiple events were not considered in the model?**

b) **Please explore a scenario using the multiple event utility values (including post event utilities) from Ara & Brazier 2010(20) for patients in the model who have a subsequent CV event.**

a) As described in response to question B2, the cost-effectiveness model does not contain health states to represent those patients having experienced multiple CV events. It was considered that a more realistic health state structure would not be advantageous, given the absence of evidence from a HoFH population from which to

derive inputs. Although this represents a limitation, there are precedents for this structure (e.g., TA385). For this reason, the utility values from Brazier & Ara (2010) were not used.

b) Due to the absence of health states to represent patients having had multiple CV events, we are unable to perform the requested scenario analysis.

B22. Priority question: For the general population utility values, the NICE methods guide recommends using the Health Survey for England (HSE) 2014 dataset, as recommended by the DSU. Please update the general population utility values model to use the HSE 2014 dataset.

A scenario that uses general population utility values based on HSE 2014 has been added. The general population utility values based on the HSE 2014 dataset are higher than derived using Equation 2 from Ara and Brazier (2010). Results using updated utility values are given in Table B22.1.

Table B22.1. Results using updated utility values (HSE 2014 dataset)

	Total			**Incremental**				
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	INMB (£)
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	5,976,577	12.84	10.05	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

B23. Please provide a scenario which explores a disutility associated with IV infusion for evinacumab.

A target search identified NICE TA898 which applied an annualised infusion-associated disutility of -0.023 for patients receiving pembrolizumab plus chemotherapy. The disutility value of -0.023 was reflective of patients with bone metastases who receive a treatment with 30-minute IV infusion regimen every four weeks. It should be noted that the EAG and Committee raised significant concerns

about the inclusion of the -0.023 disutility in TA898. The EAG noted that it was not derived using NICE's reference case methods, was derived from a general population sample and had poor face validity (appears too large). In TA898, both the EAG and Committee recommended that the disutility of IV infusion was not included in the economic evaluation. We therefore focused on priority questions and did not add this scenario.

B24. Please clarify how the source of the disutility value for LDL-apheresis was identified.

a) **Please justify why the selected source (Beaudet et al(22)) was considered appropriate? The EAG found that the source of the disutility value was from dialysis patients in Switzerland.**
b) **Please clarify if any utility data for UK haemodialysis patients are available and if so, please provide a scenario analysis using these data.**

Very few sources could be identified from which to estimate a disutility associated with apheresis and no data were identified for the UK. An estimate was made by assuming that there is some equivalence in the QoL impact between haemodialysis and apheresis. However, there are significant limitations associated with this assumption and, therefore, considerable uncertainty associated with any estimates obtained. We consider that the best approach to understanding the significance of this issue is to examine the extent to which the model results are sensitive to this input. If we were to ignore the negative QoL impact associated with apheresis, setting the disutility to zero, the results shown in Table B24.1 are obtained. This indicates that, despite the uncertainty in the estimate of the disutility, this is very unlikely to be relevant in terms of decision-making.

Table B24.1. Results assuming zero disutility associated with apheresis

Technologies	Total			Incremental				
	Costs (£)	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	INMB (£)
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Lomitapide + SoC	5,976,577	12.84	10.12	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

B25. Please clarify if EQ-5D was measured beyond 24 weeks in ELIPSE. If so, please provide these data.

EQ-5D was not measured beyond 24 weeks in ELIPSE.

B26. Please clarify if EQ-5D data were collected in the long-term extension study (R1500-CL-1719). If so, please provide these data.

EQ-5D data were not collected in the long-term extension study (R1500-CL-1719).

Resource use and costs

B27. Priority question: The EAG considers that treatment effectiveness for evinacumab obtained from the MAIC includes the efficacy of the background treatments included in ELIPSE (Table 32 of the company submission). As such, please provide a scenario using the proportions of background treatments from ELIPSE to estimate the costs of background treatments.

Firstly, as discussed in response to question B14, we do not consider that it is appropriate to view the treatment efficacy as being conditional on the background treatment. This is based on the approach to the statistical analysis of the ELIPSE trial, the scale that was chosen and the absence of any treatment effect interaction terms in the analysis.

Secondly, the current cost-effectiveness model base-case assumes patients receive the mix of background treatments observed in the ELIPSE cohort, and costs these accordingly. Therefore, the requested scenario described the current base-case and no further analyses have been performed in relation to this question.

B28. Priority question: Opinion provided by the EAG's clinical expert outlined that in UK clinical practice they would expect the proportion of patients treated with LDL apheresis to be higher and that the values used by the company in the model may be more representative of treatment in the US rather than

Europe. As a scenario please assume that 75% of HoFH patients are treated with LDL apheresis in the model and that patients do not discontinue apheresis.

A scenario in which 75% of HoFH patients are treated with LDL apheresis and no patients are discontinued has been added. Results are presented in Table B28.1.

Table B28.1. Results assuming 75% of patients being treated with LDL apheresis

	Total			Incremental				
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	**INMB (£)**
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	6,284,325	13.03	10.13	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

B29. Priority question: An NHS cost inflation index (CII) inflation factor for 2021/22 is available in the latest Personal Social Services Research Unit (PSSRU) guidance (albeit noted as provisional). Additionally Office for National Statistics consumer prices index (ONS CPI) inflation indices are available for Q1 2023. Both indices are recommended in the NICE methods guide.

a) **Please clarify why costs have been inflated to 2020 and not 2022/23.**

The cost-effectiveness model should be updated to use the latest available indices to adjust prices for inflation where appropriate. See part b) for further details.

b) **Please update the model for the cost year 2022/23.**

The additional ONS CPI inflation indices for 2021 and 2022 have been added to the model such that prices are adjusted using the most up-to-date data.

B30. Priority question: Please justify why it was deemed appropriate to include the costs of PCSK9 inhibitors for patients with a null/null mutation, even though these treatments are ineffective for this subgroup of patients. Is it

clinically plausible clinicians would prescribe knowingly ineffective treatments to HoFH patients with a null/null mutation?

The cost-effectiveness model has accounted for 76.9% of patients receiving evolocumab, based on the baseline treatment mix in the ELISPE study cohort. This should, therefore, reflect clinical practice with respect to the proportion of patients with a null/null mutation who might receive and remain on this treatment. On this basis we consider that the approach to costing of PCSK9 inhibitors is appropriate.

Clinical experts consulted during the development of this cost-effectiveness model advised that PCSK9 inhibitors would often be attempted in patients with a null/null mutation in attempt to obtain any LDL-C reduction, even if this is small. This approach is also consistent with the European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia (1). Therefore, it does not seem appropriate to assume that no patients with a null/null mutation receive PCSK9 inhibitors.

a) **The EAG's clinical experts advised that for patients with a null/null mutation, atorvastatin and ezetimibe are ineffective and would unlikely be prescribed to these patients. Therefore, please provide a scenario where the treatment effects and costs associated with atorvastatin, ezetimibe and PCSK9 inhibitors are removed from the model for the proportion of patients with a null/null mutation.**

While the efficacy of these treatments is associated with the residual level of LDL receptor function, some response may still be possible at low levels of function (1). Given the urgent need to deploy all available means in order to reduce the LDL-C concentrations in this group of patients, we were advised by clinical experts that patients would receive, and many would remain, on atorvastatin and ezetimibe. We, therefore, maintain that it is appropriate to include their effects in patients with a null/null mutation within the model.

We can consider what the likely impact of removing the efficacy of atorvastatin and ezetimibe from a subgroup of patients would be. These treatments were used more frequently in the ELIPSE trial cohort compared with the Thompson et al. study cohort. Therefore, the model adjustments, making use of the efficacy of these

treatments, has the effect of lowering the baseline LDL-C concentration (before evinacumab or lomitapide are prescribed). Removing their efficacy from a fraction of patients (with the null/null mutation) would lead to a slightly higher baseline LDL-C concentration. This would lead to a larger incremental absolute change in LDL-C concentration for evinacumab, given its superior efficacy. The current approach is, therefore, conservative in the sense that it is biased against evinacumab.

B31. Priority question: The EAG's clinical experts advised that in the UK, apheresis is delivered weekly. Therefore, please provide a scenario exploring a weekly apheresis administration frequency.

The impact on the efficacy of apheresis, expressed as the interval mean reduction in LDL-C concentration, from a change in administration frequency is unknown. Therefore, in addressing this request we have only considered the impact on the cost of apheresis. A doubling in the frequency of administration leads to a doubling in the per cycle cost of the treatment. The model results for this scenario are given in Table B31.1.

Table B31.1. Results assuming a doubling in the per cycle cost of LDL apheresis

	Total			Incremental				
Technologies	**Costs (£)**	**LYG**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (£/QALY)**	**INMB (£)**
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	6,143,653	12.838	10.05				-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

B32. Priority question: The Summary of Product Characteristics (SmPC) for evolocumab recommends patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule. Please adjust the costs of evolocumab in the model for the proportion of patients who receive apheresis.

The number of doses per cycle for evolocumab has been adjusted to reflect that patients who receive apheresis would receive 420mg evolocumab every two weeks.

B33. Priority question. For the administration cost of evinacumab, the model describes the unit cost as one hour of community nurse time at a cost of £42 per hour. Please clarify if the nurse cost obtained from PSSRU 2021(23) is for a nurse (GP practice), which is associated with a cost of £42 per hour or a Band 5 community nurse, which is £44 per hour. If neither of these categories is used, please describe what has been used from PSSRU 2021(23).

a) **Please clarify why costs from PSSRU 2022 have not been used?**

An overall unit cost for 2020/2021 for a GP practice nurse was used with a value of £42 per hour. Since the availability of the PSSRU 2022, this value should be updated to use the latest data. Therefore, the revised version of the model now uses a cost of £46 per hour for GP practice nurse. Based on a monthly frequency of administration, this equates to an annual administration cost of £552.00 for evinacumab.

B34. Priority question: The EAG's clinical experts advised that the first IV administration would be longer (two three hours) than subsequent IV administrations. Please explore a scenario where the first IV administration incurs the cost of 2.5 hours of nurse time.

The cost of nurse time used has been updated and uses the value of £46 per hour (see the response to B33). For a monthly administration visit that require 1 hour of nurse time, the annual cost is £552. If 2.5 hours is required for the first administration visit, then the annual cost is £621. The headline model results using this higher administration cost for evinacumab is provided in Table B34.1. This change leads to a small increase in incremental costs, and a small decrease in the net monetary benefit.

Table B34.1. Results using alternative administration cost for evinacumab

Technologies	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	INMB (£)
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	5,976,577	12.84	10.05				-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

B35. Priority question: In the economic model (tab 'Cost data', cell J35), an administration cost of £69.82 has been applied for lomitapide. The name and reference for the cost in the model (tab 'Control', cells A206 and D206) states this is an additional monitoring cost based on data from http://www.juxtapid.com/prescribing-information & National tariff payment system documents 2022., but it is not described in the company submission

a) **In the company submission it is stated that an administration cost is not assumed for lomitapide. Please clarify the cost included in the model.**

In the original version of the cost-effectiveness model, the column containing J35 was misleadingly labelled administration costs. The value entered into J35 for lomitapide does, indeed, reflect the monitoring cost for lomitapide and not administration – for which no cost is assumed. This column has been renamed in the revised version of the model to avoid confusion.

b) **Please provide a scenario which excludes the administration cost for lomitapide.**

There is no cost applied in relation to the administration of lomitapide. The cost in cell J35 was misleadingly labelled, suggesting that it was related to administration. This has now been corrected in the revised version of the model (see also response in B35 a). Therefore, no additional scenario analyses have been performed in response to this question.

B36. Priority question: In the company submission, monitoring costs for lomitapide should reflect those presented in Table 44, but these are not included in the model. The EAG's experts agreed with additional monitoring assumptions for lomitapide. Please clarify if the additional monitoring costs associated with liver function tests and Fibroscan (£57.30 in the 1st year and £58.45 in subsequent years) should be included for lomitapide in the company base case and if so, please correct the model.

The value that was previously used within the cost-effectiveness model to capture the additional monitoring costs of lomitapide was incorrect. This should have been aligned with the data presented in Table 44 as noted in this question. The revised cost-effectiveness model base-case has been updated to make use of the correct value for the additional monitoring costs required for lomitapide. This is composed of 1 Fibroscan and 2 additional liver function tests in year 1 and 3 in subsequent years. Using the unit costs from NHS reference costs schedule 2021/22, (Fibroscan, £88; liver function test, £1.40), this additional cost is £90.80 in year 1 and £92.20 in subsequent years. In the cost-effectiveness model, it is not possible to implement differential treatment-specific monitoring in first and later years. Therefore, only the value for subsequent years has been applied across all years.

B37. Priority question: Please clarify why monitoring costs associated with blood tests are not sourced from NHS reference costs? Please provide a scenario using diagnostics costs (for example NICE Diagnostics Assessment Programme (DAP)S08 - phlebotomy) from NHS reference costs 2021/22.

Based on the NHS reference costs schedule 2021/22, the national average unit cost for phlebotomy services (DAPS08) is £4.70. A scenario in which monitoring costs associated with blood tests were set to be £4.70 (inflated to 2022 price level) has been added. Results are presented in Table B37.1. The results of the scenario analysis demonstrate that the results of the analysis are robust to the source of monitoring costs.

Table B37.1. Results using alternative monitoring costs associated with blood tests

Technologies	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	INMB (£)
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	5,976,708	12.84	10.05				-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

B38. Priority question. Please update the Fibroscan cost (RD48Z) to be the latest cost from the NHS reference costs schedule 2021/22.

Based on the NHS reference costs schedule 2021/22, the unit cost of Fibroscan is £88. This change has been applied in the revised version of the cost-effectiveness model provided.

B39. Priority question: The EAG's clinical experts advised that HbA1c tests would be performed annually for HoFH patients. Please explore a scenario where the cost of an annual HbA1c test is included as part of the monitoring costs.

An appropriate cost estimate to use for HbA1c monitoring is the cost of £4.70 for phlebotomy services (DAPS08), mentioned in response B37. Including this cost annually, for both lomitapide and evinacumab, is certain to have a negligible impact on the incremental costs. We have, therefore, chosen to prioritise other questions and have not presented the results of this scenario analysis.

B40. Priority question: The EAG's clinical experts advised that the monitoring resource use assumptions included in the model are not reflective of UK clinical practice and instead proposed alternative assumptions, presented in the below table. Please provide a scenario implementing the EAG's clinical expert assumptions for monitoring resource use.

Resource use	First year	Subsequent years

Blood sample appointment	3	2
GP appointment	2	2
Specialist appointment	4	2
Total cholesterol	3	2
HDL cholesterol	3	2
Liver transaminase (ALT or AST)	3	2

A scenario was implemented using EAG's clinical expert assumptions for monitoring resource use. Inputs used in this scenario are presented in Table B40.1 and results in Table B40.2. These results indicate that the results of the evaluation are robust to the assumptions regarding the frequency of treatment monitoring.

Table B40.1. Monitoring costs calculating using alternative assumptions for monitoring resource use

Resource use	Year 1	Subsequent years	Costs	Source
Routine appointments				
Blood sample appointment	3	2	£9.04	Inflated to 2022 price level using CPI data from ONS
GP appointment	2	2	£64.36	
Specialist appointment	4	2	£113	PSSRU 2022
Blood tests				
Total cholesterol	3	2	£1.40	Assumptions, NICE TA385
HDL cholesterol	3	2	£1.40	
Liver transaminase (ALT or AST)	3	2	£1.40	
Total annual monitoring costs (first year)				£620.44
Total annual monitoring costs (subsequent years)				£381.20

Abbreviations: ALT. alanine transaminase; AST, aspartate aminotransferase; GP, general practitioner; NICE, national institute for care and health excellence.

Note: an additional annual cost of £92.20 is included for extra blood test and ultrasound elastography for lomitapide

Table B40.2. Results using alternative monitoring frequency

Technologies	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	INMB (£)
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	5,979,757	12.84	10.05				-	-
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.								

B41. Priority question: The EAG considers that the company has used health state costs from TA694(15) without fully explaining the rationale behind the choice or explanation of the assumptions underlying the costs. Additionally, it does not appear that the company has taken on board the EAG critique of the health state costs in TA694(15).

a) **Please fill out the table at the end of this question..**

b) **Please clarify if combined primary and secondary incremental costs from Danese *et al*.2016(24) were used for first and recurrent events and if so, please justify this assumption.**

c) **Acute costs in Danese *et al*.2016(24) represent a 6-month cost, yet the model cycle length is one-year. Please clarify why an adjustment for acute costs to reflect the model cycle was not implemented.**

d) **The EAG in TA694(15) preferred stroke costs from TA393(21) (£8,618 for acute stroke and £1,769 for post-stroke in 2013/14 prices). Please clarify why these costs were not used for the company base case.**

e) **The EAG notes that the cost of CVD death used by the company in TA694 was a cost saving of £236.11. Additionally, the EAG for TA694 disagreed with using a cost saving for CVD deaths and instead preferred to use the total cost of CVD death estimate available in CG181 (in TA694, this was £1,220 in 2019 prices). Please clarify if the cost of CVD death**

included in the model was obtained from TA694, but assumed not to be a cost saving and then inflated to 2020 prices.

f) Please provide a scenario incorporating the following assumptions for health state costs:

- **Primary and secondary event incremental costs are used (reflecting the EAG preferred approach of modelling both primary and secondary prevention populations, as requested in B1).**
- **Adjust acute event health state costs in the model to reflect the one year model cycle. Please note that the 7-36 months costs in Danese *et al*.2016 are annualised.**
- **Replace stroke costs with those preferred in TA393 (£8,618 for acute stroke and £1,769 for post-stroke in 2013/14 prices), inflated to 2023 prices.**
- **use the cost of CVD death from NICE clinical guideline (CG)181, inflated to 2023 prices.**

a) We have completed the table below as requested in this question. However, the costs have been inflated to 2022 prices, in line with other cost inputs and using the latest available indices. The costs for stroke and post-stroke have also been updated as described in part d.

Health state	Unit cost (£)	Inflated cost (£, 2022 prices)	Source
Stable angina	7,907	9,760	CG181(25)
Post-stable angina	245	303	CG181(25)
Unstable angina	2,469	3,048	TA694 (Danese *et al.*2016) (24)
Post-unstable angina	381	471	TA694 (Danese *et al.*2016) (24)
MI	4,862	6,001	TA694 (Danese *et al.*2016) (24)

Post-MI	980	1,210	TA694 (Danese *et al.*2016) (24)
Stroke	8,618	12,254	TA393
Post-stroke	1,769	2,515	TA393
TIA	2,011	2,483	TA694 (Danese *et al.*2016) (24)
Post-TIA	810	1,000	TA694 (Danese *et al.*2016) (24)
CV death	-236	-291	TA694 (Danese *et al.*2016) (24)

b) This is correct. For deriving the costs of some CV events, the cost-effectiveness model has used the costs for first and second events combined from Danese et al. (2016). We are aware of the discussion regarding the possible advantages and disadvantages of using combined versus disaggregated costs for primary and recurrent events from the critique of TA694. However, the structure of the current cost-effectiveness does not distinguish between first and subsequent CV events. Therefore, the health states represent a mixture of first and subsequent events and it is then natural to apply the combined costs from Danese et al. (2016).

Furthermore, we also note the potential limitations of using the first and second event cost data as described in the company response in TA694. This included i) that first and second event costs are generally consistent, ii) combined events costs benefit from increase sample size, and iii) the counter-intuitive observation that some first event costs are higher than for subsequent events.

c) The appropriate adjustments were made using the data from Danese et al. such that these costs can be applied to a 1-year model cycle. The cost for the first year was obtained as the cost for the acute phase (6-month cost) plus half of the annualised mean cost from months 7-36.

d) Our aim was to source health state costs from the minimum number of separate sources, where possible, such that there may be greater consistency amongst the cost estimates. However, based on the critique of TA694, we recognise that the

values for stroke currently used in the cost-effectiveness model base-case are likely to be criticised as being lower than expected. Therefore, the revised version of the cost-effectiveness model base-case now makes use of the acute and post-event stroke costs from TA393, inflated to 2022 prices.

e) It is correct that the current cost-effectiveness model has replicated the approach taken in TA694, and that the cost saving for CV death has erroneously been applied as a positive cost. However, we do not consider that this approach is inappropriate, and we have only modified the model base-case to use the correct (negative) cost. Our reasoning mirrors the company response to this critique in TA694. The time horizon is the patient's lifetime and should a CV death incur relatively lower healthcare costs than a non-CV death, then it is not inappropriate to model this as a negative incremental cost on CV death.

Economic systematic literature reviews

B42. For the utility and cost systematic literature reviews (SLRs) presented in company submission Appendix H and I, please clarify if quality assessment of the studies were performed and if so, describe the methods.

The economic SLRs identified 2 relevant HRQoL studies and 2 HRU studies, with 1 study belonging to both these categories, so 3 studies identified in total. No cost-effectiveness studies were identified. The identified studies were assessed narratively in Appendix H.3 and I.3, and data were tabulated according to NICE guidance to companies (26) in Table 11 and Table 15 of the Appendices. This guidance does not stipulate the use of critical appraisal tools for these study types.

Data from the identified studies were deemed not to be suitable for use in the submission itself.

B43. Please clarify why the time limit for the economic evaluation and cost/resource SLRs was 2010 onwards.

Treatment in the field of hyperlipidaemia management generally, and HoFH specifically, have evolved rapidly over the past two decades, with for instance,

lomitapide having only become available since 2013. For this reason, identification of studies reporting on HRU costs prior to 2010 were deemed to lack relevance, because:

- New treatments will have become available, with treatment pathways changing and indeed the whole paradigm of lipid management having evolved.
- Unit costs will have materially changed during before this time. This cannot be accounted for by simply inflating costs, as, for instance, some drugs will have become generic.

Section C: Textual clarification and additional points

C1. Priority question. Please clarify the outcome reported in the forest plots presented in Figure 1 (Subgroup analysis of randomisation stratification parameters (region, LDL apheresis) in ELIPSE) and Figure 2 (subgroup analysis of patient demographics in ELIPSE) of company submission Appendix E.

The outcome is the primary outcome of the ELIPSE trial, percent change in LDL-C level from baseline at 24 weeks.

C2. Priority question. Baseline LDL-C from ELIPSE is said to be 6.71mmol/L in the company submission (pg 56, 124) but in the model it is 6.597mmol/L. Please clarify which is correct?

The value of 6.71mmol/L is for all patients in both arms of the EIPSE trial, while 6.597mmol/L is for the evinacumab arm only. The former would be the relevant value; however, this is not an input to the cost-effectiveness model. The model uses the baseline LDL-C from Thompson et al. (2015) study cohort since it is this cohort from which the baseline risk is modelled.

C3. The BNF prices for atorvastatin 80 mg and ezetimibe 10 mg are £1.40 and £1.53, respectively. Please update the model with the correct prices.

The base case model input has been updated to reflect drug costs for atorvastatin and ezetimibe.

C4. Please provide instructions on how to run scenarios 2, 3 and 9 as the EAG were unable to replicate the company results presented in B.3.10.3.2.

Scenario 2: Lower patient body weight. There was an error in the previous model, now corrected in the revised version. The parameters of the log-normal distribution for patient body weight should be calculated based on the inputted mean weight and the standard deviation. However, this had been overwritten with the calculated value, such that changing the patient body weight inputs did not change the log-normal distribution parameters used to calculate the dosage of evinacumab.

Scenario 3: Assume for evinacumab no unused vial wastage. This scenario can be obtained using the dropdown menu on the 'Model settings' sheet in row 88. The model base-case uses 'no vial sharing' and assumed that any used evinacumab volume is discarded. This scenario uses 'full vial sharing' and assumes that any unused volume is retained for the next patient.

Scenario 9: Evinacumab discontinuation 50% of lomitapide. The short-term discontinuation proportion for lomitapide is 13.8% based on the results of the clinical trial (Cuchel et al. 2013). This scenario assumes a short-term discontinuation proportion of 7% for evinacumab. The scenario name is slightly misleading since this value is not precisely 50% of the value for lomitapide. By setting the input in cell D40 in 'Clinical data' sheet to 7%, the results of this scenario analysis will be obtained.

C5. Please clarify if the set of transition probabilities in cell C8 of the TPs tab of the economic model is incorrectly labelled as the comparator and should instead reflect baseline values (table CV risk, BU20:CP123).

This is correct, tab 'TPs' cell should be labelled as baseline which reflect the background TPs.

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Appendix: Updated based-case results

Updated base-case cost-effectiveness results

Table 1. Updated base-case results

Technologies	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	**INMB (£)**
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	5,976,577	12.84	10.05	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

Table 2. Summary of disaggregated results of the updated base-case analysis.

Outcomes	Technology		Incremental
	Evinacumab + SoC (£)	**Lomitapide + SoC** (£)	(£)
Costs			
Drug costs	[redacted]	5,960,550	-[redacted]
Monitoring costs	1,875	1,829	46
Health state costs	14,119	14,198	-79
CV death costs	-2,801	-2,914	113
Total costs	[redacted]	5,976,577	[redacted]
Health outcomes			
Life years	[redacted]	12.84	[redacted]
QALYs	[redacted]	10.05	[redacted]

Abbreviations: CV, cardiovascular; QALYs, quality-adjusted life years; SoC, standard of care.

Updated based-case probabilistic sensitivity analysis

Table 3. Updated Base-case probabilistic results.

	Total			Incremental				
Technologies	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	INMB (£)
Evinacumab + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Lomitapide + SoC	6,029,571	12.96	10.12	-	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; SoC, standard of care.

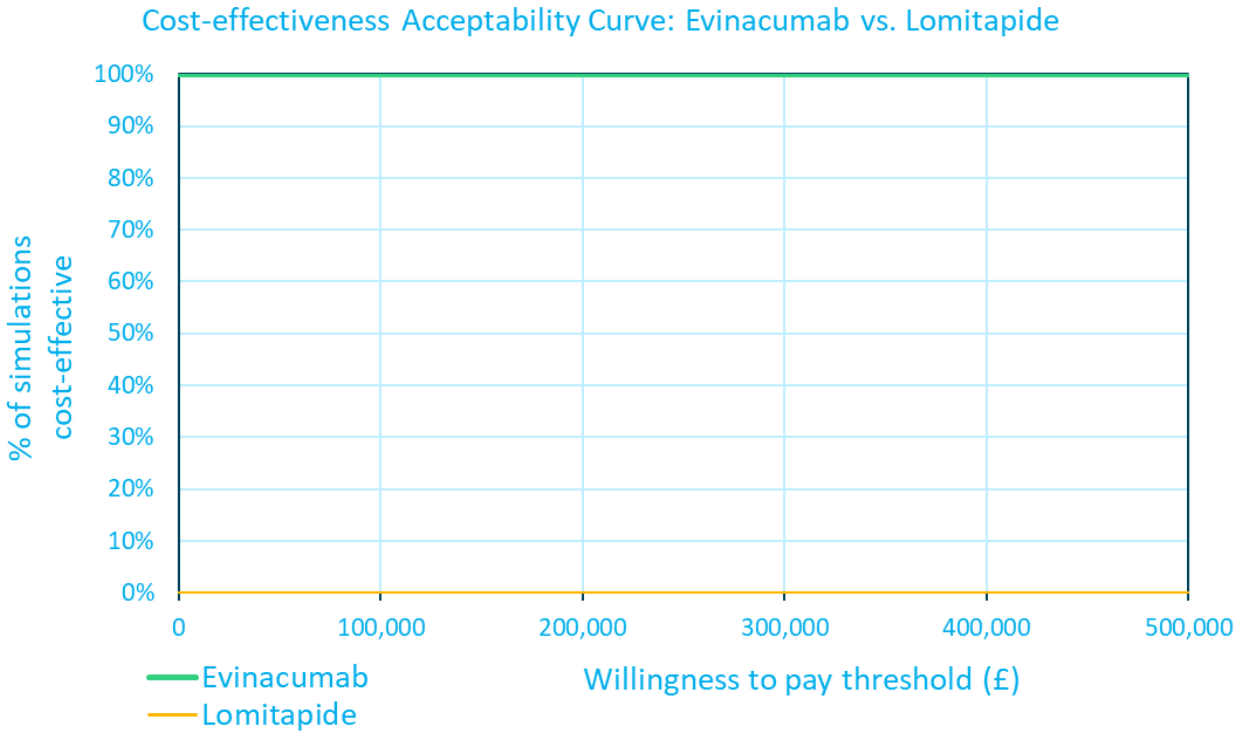
Table 4. Summary of disaggregated results of the updated probabilistic base-case analysis.

Outcomes	Technology		Incremental
	Evinacumab + SoC	Lomitapide + SoC	
Costs			
Drug costs	[redacted]	£6,013,487	[redacted]
Monitoring costs	£1,884	£1,843	£41
Health state costs	£14,140	£14,241	-£101
CV death costs	-£2,744	-£2,846	£103
Total costs	[redacted]	£6,029,571	[redacted]
Health outcomes			
Life years	[redacted]	13.02	[redacted]
QALYs	[redacted]	10.18	[redacted]

Abbreviations: CV, cardiovascular; QALYs, quality-adjusted life years; SoC, standard of care.

Figure 1. [redacted] – updated base-case

Figure 2. Cost-effectiveness acceptability curve – updated base-case



Updated based-case deterministic sensitivity analysis

Table 5. Updated deterministic sensitivity analysis results.

Parameter	INMB - at lower value of parameter (£)	INMB - at upper value of parameter (£)
Demographics: Cohort baseline age (11.6, 72.4)	[redacted]	[redacted]
Baseline risk: Gompertz (Thompson 2015) Rate (-4.45, -7.42)	[redacted]	[redacted]
Baseline risk: Gompertz (Thompson 2015) Shape (0.04, 0.07)	[redacted]	[redacted]
Discontinuation short-term: Lomitapide (0.10, 0.17)	[redacted]	[redacted]
Demographics: baseline LDL-C level imputed (Thompson 2015) (3.5, 16.9)	[redacted]	[redacted]
Demographics: Patient weight - mean (67.7, 77.7)	[redacted]	[redacted]
Efficacy: LDL-C proportional reduction (Lomitapide) (0.29, 0.51)	[redacted]	[redacted]
Patient % of vial acceptable underdose (0%, 30%)	[redacted]	[redacted]
RR in cardiac events due to previous events (UA, US, MI) (1.00, 2.09)	[redacted]	[redacted]
Efficacy: LDL-C proportional reduction (Evinacumab) (0.38, 0.72)	[redacted]	[redacted]

Abbreviations: INMB, incremental net monetary benefit; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RR, relative risk; SA, stable angina; UA, unstable angina.

Figure 3. Tornado diagram – updated base case

Updated base-case scenario analysis

Table 6. Results of the updated base-case analyses.

ID	Scenario	Incremental costs	Incremental QALYs	INMB (£)	Relative change from base-case INMB (%)
-	Base case	[redacted]	[redacted]	[redacted]	
1	Apheresis efficacy LDL-C reduction 50.4% (Pottle *et al.* (2019))	[redacted]	[redacted]	[redacted]	-0.6%
2	Patient lower mean body weight of 60kg	[redacted]	[redacted]	[redacted]	14.4%
3	Assume for evinacumab no unused vial wastage	[redacted]	[redacted]	[redacted]	12.8%
4	Evinacumab given on 4-weekly rather than monthly basis	[redacted]	[redacted]	[redacted]	-8.3%
5	Evinacumab underdosed up to 20% based on target weight	[redacted]	[redacted]	[redacted]	5.2%
6	Choice of survival function: Log-logistic distribution	[redacted]	[redacted]	[redacted]	27.5%
7	Alternative utility source: TA395	[redacted]	[redacted]	[redacted]	0.0%
8	Alternative cost source: TA395	[redacted]	[redacted]	[redacted]	0.1%
9	Evinacumab discontinuation 50% of lomitapide	[redacted]	[redacted]	[redacted]	6.6%
10	Link between 1 mmol/L LDL-C change and CV rate reduction alternative source (Navarese *et al.* (2015))	[redacted]	[redacted]	[redacted]	8.6%
11	Link between 1 mmol/L LDL-C change and CV rate reduction alternative source (Navarese *et al.* (2018))	[redacted]	[redacted]	[redacted]	-4.6%

12	Assuming 1.5% discount rate for costs and utilities	[redacted]	[redacted]	[redacted]	25.9%
13	Evinacumab efficacy 50.9% (ELIPSE RCT vs placebo with lomitapide patients removed)	[redacted]	[redacted]	[redacted]	0.6%
14	EAG Scenario B1.1 (Distributing patients across health states at baseline)	[redacted]	[redacted]	[redacted]	-1.3%
15	EAG Scenario B1.1 + B9.1	[redacted]	[redacted]	[redacted]	-0.7%
16	EAG Scenario B1.1 + B9.2	[redacted]	[redacted]	[redacted]	-1.9%
17	EAG Scenario B1.1 + B9.3	[redacted]	[redacted]	[redacted]	-0.9%
18	EAG Scenario B1.1 + B9.4	[redacted]	[redacted]	[redacted]	-1.7%
19	EAG Scenario B6.1 (Lower non-fatal to fatal incidence event ratio)	[redacted]	[redacted]	[redacted]	16.8%
20	EAG Scenario B6.2 (Higher non-fatal to fatal incidence event ratio)	[redacted]	[redacted]	[redacted]	-10.5%
21	EAG Scenario B7.1 (20% higher proportion of cardiac events in all CV events)	[redacted]	[redacted]	[redacted]	0.0%
22	EAG Scenario B9.1 (Lower relative risk of CV mortality for cardiac events)	[redacted]	[redacted]	[redacted]	0.5%
23	EAG Scenario B9.2 (Higher relative risk of CV mortality for cardiac events)	[redacted]	[redacted]	[redacted]	-0.5%
24	EAG Scenario B9.3 (Lower relative of CV mortality for cerebrovascular events)	[redacted]	[redacted]	[redacted]	0.4%

25	EAG Scenario B9.4 (Higher relative risk of CV mortality for cerebrovascular events)	[redacted]	[redacted]	[redacted]	-0.3%
26	EAG Scenario B13.1 (Cost minimisation analysis of evinacumab versus lomitapide)	[redacted]	[redacted]	[redacted]	4.0%
27	EAG Scenario B19.1 (Removing age adjustment multipliers from health state utility values)	[redacted]	[redacted]	[redacted]	0.0%
28	EAG Scenario B20.1 (Alternative utility value of 0.721 for MI)	[redacted]	[redacted]	[redacted]	0.0%
29	EAG Scenario B22.1 (Using HSE 2014 general population utility values)	[redacted]	[redacted]	[redacted]	0.0%
30	EAG Scenario B24.1 (Assuming zero disutility associated with apheresis)	[redacted]	[redacted]	[redacted]	0.0%
31	EAG Scenario B28.1 (Assuming 75% patients on background apheresis treatment)	[redacted]	[redacted]	[redacted]	1.9%
32	EAG Scenario B31.1 (Assuming apheresis is given weekly)	[redacted]	[redacted]	[redacted]	-0.1%
33	EAG Scenario B34.1 (Assuming the first IV administration last for 2.5 hours for evinacumab)	[redacted]	[redacted]	[redacted]	0.0%
34	EAG Scenario B37.1 (Alternative source for cost of blood tests)	[redacted]	[redacted]	[redacted]	0.0%
35	EAG Scenario B40.1	[redacted]	[redacted]	[redacted]	0.0%

	(More frequent monitoring appointments and tests)				

Abbreviations: CV, cardiovascular; INMB, incremental net monetary benefit; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; RCT, randomised controlled trial.

Cells shaded green indicated evinacumab is cost-effective in this scenario cells shaded in red indicate evinacumab is not cost-effective in this scenario.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Clarification questions

Clarification response appendix for Question A16:

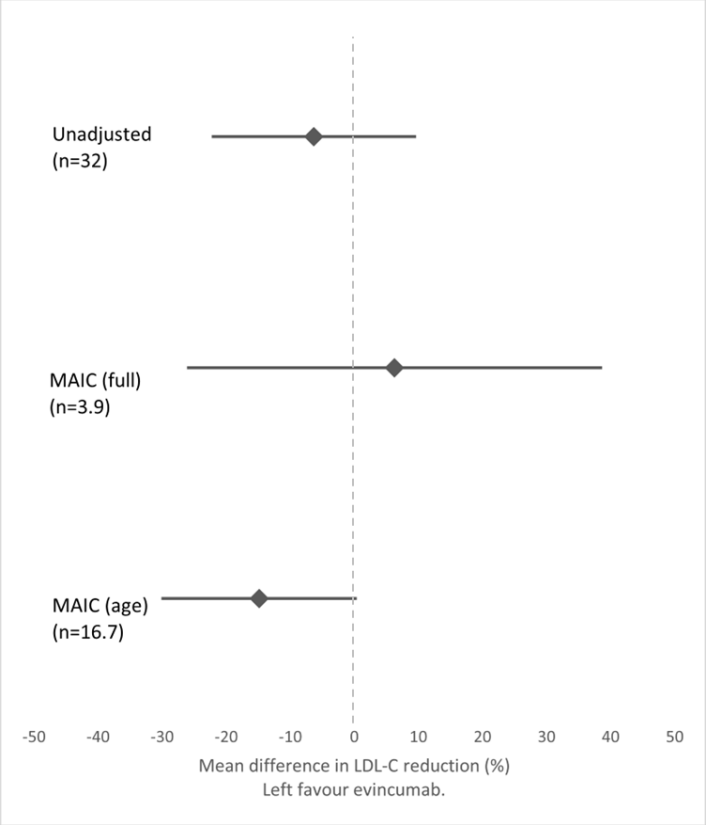
The correct mean difference data for the ELIPSE cohort with lomitapide patients removed should read as in the updated table:

Method	Matching variables	Evinacumab N/ESS	Lomitapide N/ESS	Mean (95% CI) evinacumab	Mean (95% CI) lomitapide	Mean Difference (95% CI) evinacumab vs lomitapide
Unadjusted naïve ITC	NA	32.0	29.0	-46.42 (-57.62 to -35.23)	-40.1 (-51.47 to 28.73) [a]	-6.32 (-22.7 to -9.63)
MAIC	Age, CHD, LDL-C	3.9	29.0	-33.83 (-96.84 to 29.17)	-40.1 (-51.47 to 28.73) [a]	6.27 (-26.1 to 38.64)
MAIC (sensitivity analysis)	Age	16.7	29.0	-54.94 (-65.16 to -44.72)	-40.1 (-51.47 to 28.73) [a]	-14.84 (-30.08 to 0.4)

Key: CHD, coronary heart disease; CI, confidence interval; ESS, effective sample size; ITC, indirect treatment comparison; LDL-C, low-density lipoprotein cholesterol; MAIC, matching-adjusted indirect comparison; N, number of patients; NA, not applicable.

Note: [a] Data presented to no decimal places because that is what is reported in Cuchel et al. 2013.

This is represented below in the Forest plot.



To confirm, positive mean difference values favour lomitapide. So, in the fully matched MAIC, lomitapide is slightly more effective at reducing LDL-C compared with evinacumab. However, please note the large confidence intervals are caused by the small sample size (ESS = 3.9) and the non-significance of this result. Also note that these values were not rejected because lomitapide appeared to be more effective, they were excluded on the basis the data were unstable and using these values would effectively discard nearly all the valuable trial data collected by ELIPSE.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over ID2704

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology 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

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- 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.

NICE National Institute for Health and Care Excellence

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 tools and events, 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, a Primary Care Education Programme and a Tackling Cholesterol Together partnership with the NHS and AHSNs and other networking events for clinicians, researchers, GP's, nurses and dietitians. The charity is funded through traditional fundraising sources i.e. sponsored runs and walks, Trust and Foundation grants and legacies. Also corporate organisations, including food, diagnostic and pharmaceutical companies.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Ultragenyx £4,000 Sponsorship of HEART UK annual scientific conference July 2023 Amgen £68,452.61 Sponsorship of CVD Collaborative 2022 and 2023, HEART UK annual scientific conference, Participation in an Amgen meeting plus expenses, Scotland round table event and interview recording regarding the event. Daiichi Sankyo £145,920.00 Sponsorship of CVD Collaborative 2022 and 2023, Primary Care Education Programme 2022 and 2023, Cardio Connect, Donation, HEART UK Annual Scientific Conference Amryt £52,913.00 HoFH community building event and HEART UK Annual Scientific Conference
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients	We spoke to one Ambassador patient and one Ambassador carer, plus used our own knowledge from working in the area and our helpline.

and carers to include in your submission?	

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Carer experience:** As a mum of two boys, both with the condition I can only describe the journey as a rollercoaster. After two years and an immense battle, I finally got a diagnosis. Throughout this period, I was called a neurotic mum, I was told to go home and pop a xanthoma on my son's arm, then we got a misdiagnosis of a rare eye condition from another consultant. It wasn't until I paid to see a private paediatric dermatologist who finally listened to me, took me seriously and our medical history (both my mother-in-law and husband have FH.) From this point we have been well cared for at the Metabolic centre in Manchester's children's hospital where we have had the right care. This doesn't go without challenges themselves. Liver functions not so good due to all the medications and prior to this being asked to meet with transplant specialists. Having children growing up with this condition teaching them to eat right is difficult plus ensuring that they take their medication daily. **Patient experience:** I was diagnosed at the age of 8. The biggest challenge was getting access to treatment as the funding wasn't available, this took a lot of effort and time from consultants to negotiate and find the funding. I started plasma exchange treatment at age 11 and lipoprotein apheresis at 13. The diet has always been a real challenge. Having plasma exchange and lipoprotein apheresis took a lot of time out the your day, not just for the treatment itself but also for the consultant discussions and travel to and fro, I had to get 2 trains or 2 buses to get to the location for my treatment. Where to have the treatment was a challenge, I was treated in the renal unit and they had good experience of application of the fistula. My journey from paediatrics to adult services wasn't so bad as the consultant had treated my father so knew the family. I had to see two consultants, a lipidologist and a renal consultant each week before the treatment. I am currently on Lomitipide and atorvastatin and this is working but the gastro side effects are unpleasant.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**Carer:** Current treatment wise, I have one son who has been on Repatha for the past several years. (He was unable to tolerate Atorvastatin and now takes Rosuvastatin but did not see a reduction as good as my eldest son on Atorvastatin.) My eldest who is nearly 18, I have had to battle to get him the injection as he was a couple of points below the threshold. This child has taken Atorvastatin 80mg alongside with Ezetimibe for many years. I have found this to be very frustrating as knowing there is an alternative out there that perhaps could have allowed him to lower his numbers and even drop his Atorvastatin dose as his liver function has been affected. I feel for HoFH patients, when looking at new drugs and having such a rare form, the whole patient's medical history should be taken into consideration and not just the overall cholesterol LDL number. Over the years I have had discussions with regards to apheresis, even liver transplants, however I felt this was not suitable for my children. If only my son was given the opportunity to take Repatha earlier this would have saved time and effort of the doctors and perhaps helped with his liver function. Another point I would like to raise is with regards to my eldest son. As he reaches 18 I am also highly concerned on the level of care in the adult hospital. I haven't had an appointment or follow up since pre covid. We have discussed transition, but are yet to meet since this was brought to my attention early at the start of 2023. The advances are excellent it's just getting the drugs to the right patients. I appreciate cost is a factor but when you have rare genetics and have so many daily challenges with food, medication, liver conditions etc… I would hope they would be prescribed new advanced drugs to give the patient a better quality of life and not just necessarily on LDL numbers. **Patient:** I support what the carer has said. If there are new treatments with good efficacy they should be available to patients. The focus on LDL should not be the only thing. I was fortunate with as the QE at Birmingham is good. Repatha didn't work for me, you need the will power to inject yourself, but sadly the treatment wasn't effective. Lomitapide was prescribed and this has been quite effective. Even the consultant and pharmacists do focus on the LDL and encourage bigger doses to help reduce the LDL. Less focus on LDL and more on the impact on life would be welcome. The side effects can have such a big impact on life. The long term effects is a concern i.e. affecting liver function needs to be considered. The approach should be holistic as need to consider liver degradation.

8. Is there an unmet need for patients with this condition?	**Carer**: As discussed in previous points. **Patient:** Patients need to be aware of all available options for treatment. There is a waterfall from statins and all the way to apheresis. However, this is about what will work for each patient. People being identified as early as possible is a challenge. Healthcare professionals need to be able to identify the condition. Transition from paediatrics to adult can be a challenge. It was a bit strange as I was treated in the dialysis unit as no apheresis unit was in Birmingham and the renal consultants also had challenges with space. When I moved to adult care there were discussions about where I should be treated. So there were logistics issues and I landed up at Tipton which meant that I had to get 2 trains or 2 buses to get there. Also I had to have 2 appointments, one with the lipidologist and another with the renal consultant every week.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**Patient:** If already an apheresis patient, this treatment would be beneficial as it could reduce the regularity or the need for apheresis. If this could be done at home this would be really beneficial. This treatment sounds really promising. Whilst personally Lomitapide is good for me, I don't have to go to a place for treatment or worry about needles. The side effects of Lomitapide are not good and also the long term effects on the gut health are worrying. So if this is an alternative it could be considered.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	**Patient:** The side effects would need to be assessed both short and long term and how this compares to other treatments. A patient would need to consider the time and cost of travel and also the time to sit through the infusion. However, it appears that the advantages may outweigh the disadvantages.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	**Patient:** 1. Any patient having treatment that isn't particularly effective i.e. not reducing LDL or fitting with lifestyle 2. A patient on apheresis as this seems an improvement on this, if the reduction is equal or greater than apheresis. However, this is difficult to say unless the treatment is available

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Patient:** Costs of travel and if too far for people to travel. Eligibility of people being almost meeting threshold but not quite would exclude them from benefitting from this treatment. The different experiences in different locations i.e. Birmingham may have an easier journey than in another area, so potentially creating a postcode lottery

Other issues

13. Are there any other issues that you would like the committee to consider?	HEART UK would support all these comments. We have a big concern about a postcode lottery as we hear on the helpline that people do have difficulty with accessing treatments, sometimes because of funding and sometimes because of not meeting the eligibility criteria. We have heard some patients telling us that their consultant informs them they can only have certain treatment if they either have a heart attack or have another heart attack or on occasions there is a suggestion a patient stops a medication they are already taking so their LDL increases to enable them to get access to a treatment. A consistent approach to access and flexibility around eligibility criteria is essential i.e. not just looking at the LDL but using the holistic approach to consider the whole patient, their life and impact now and in the future.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Treatment delivery point is important • Consistent access to treatment • Consistent treatment and a smooth transition between paediatric and adult clinics • The holistic approach and not just looking at the LDL number i.e. long term impact • Having another choice of treatment as a HoFH patient would be a real benefit

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over ID2704

Professional organisation submission

Thank you for agreeing to give us your organisation's 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.

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.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	HEART UK – The Cholesterol Charity
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	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 tools and events, 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, a Primary Care Education Programme and a Tackling Cholesterol Together partnership with the NHS and AHSNs and other networking events for clinicians, researchers, GP's, nurses and dietitians. The charity is funded through traditional fundraising sources i.e. sponsored runs and walks, Trust and Foundation grants and legacies. Also corporate organisations, including food, diagnostic and pharmaceutical companies.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Ultragenyx £4,000 Sponsorship of HEART UK annual scientific conference July 2023 Amgen £68,452.61 Sponsorship of CVD Collaborative 2022 and 2023, HEART UK annual scientific conference, Participation in an Amgen meeting plus expenses, Scotland round table event and interview recording regarding the event. Daiichi Sankyo £145,920.00 Sponsorship of CVD Collaborative 2022 and 2023, Primary Care Education Programme 2022 and 2023, Cardio Connect, Donation, HEART UK Annual Scientific Conference Amryt £52,913.00 HoFH community building event and HEART UK Annual Scientific Conference
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. To reduce the onset and progression of atherosclerotic cardiovascular disease. As the overriding risk factor for CVD in homozygous FH is markedly elevated LDL, the aim is therefore to lower this as much as possible. There is evidence that lower LDL in homozygous FH leads to better outcomes, including mortality 2. To reduce aortic root disease and cardiac valve disease that is difficult to treat in particular aortic stenosis in patients with aortic root extensive atherosclerotic disease. https://academic.oup.com/eurheartj/article/39/14/1162/3896244 https://www.atherosclerosis-journal.com/article/S0021-9150(16)31420-4/fulltext Aim for LDLc<1.8 mmol/l in high risk and <1.4 mmol/l in very high risk patients.
7. 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.)	Reduction in LDLc by 15% (over and above the biological variability)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, most patients do not get to LDL-c target despite conventional therapy due to a number of reasons (lomitapide: tolerability and liver function, apheresis: challenges with venous access, geographical access, time burden, only 7 centres in UK offers lipoprotein apheresis and there is a capacity issue with accommodating more patients etc).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Selected Tertiary centres,
9a. Are any clinical guidelines used in the	NICE CG71, Heart UK statement, EAS statement Links to HEART UK statement https://www.atherosclerosis-journal.com/article/S0021-9150(16)31420-4/fulltext

treatment of the condition, and if so, which?	Link to European Atherosclerosis statement https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehad197/7148157?login=false
9b. 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.)	Pathway is well defined. Agreed among clinicians in UK https://www.atherosclerosis-journal.com/article/S0021-9150(16)31420-4/fulltext
9c. What impact would the technology have on the current pathway of care?	It would be an additional option for LDL cholesterol lowering in homozygous FH, particularly where the other two options are not clinically applicable due to some of the issues states in part 8.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently used
10a. How does healthcare resource use differ between the technology and current care?	The technology will provide another option for treating this severe genetic disorder. Only ~70-80 patients with HoFH in UK are recognized in UK (represents a survivor cohort). Less than half of these patients with severe phenotype, intolerant to other therapies or can't access lipoprotein apheresis (distance, vascular access, cannot tolerate because of CHD and valve disease) will need this treatment. Aggressive LDL-C lowering treatment should be adopted as soon as possible. https://pubmed.ncbi.nlm.nih.gov/27017151/ https://pubmed.ncbi.nlm.nih.gov/19026292/
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary care -secondary care clinics with experience of treating homozygous FH patients. For example centres who are already providing lipoprotein apheresis, Lomitapide and high dose PCSK9 monoclonal antibodies.
10c. What investment is needed to introduce the	Lipid specialist nurse training in use of the technology. Initially the medicine would be given in a hospital setting. If well tolerated, this could then be administered in a home setting with home care.

technology? (For example, for facilities, equipment, or training.)	Time for consultant Lipidologists in these centres for follow up and monitoring.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the trials show a 40-50% reduction in LDL-c which translates to very large clinical impact. This reduction in LDL-C is very important to avoid future complications like CHD, other ASCVD like PVD, aortic valve disease and aortic root disease, even more than what is expected for general population as the only risk factor for ASCVD in these patients is very high cholesterol.
11a. Do you expect the technology to increase length of life more than current care?	Yes. There is evidence that lower LDL in homozygous FH leads to better outcomes, including mortality https://academic.oup.com/eurheartj/article/39/14/1162/3896244
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No but makes sense to target those with most unmet need and highest risk - i.e patients with homozygous FH.

The use of the technology

13. 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	Likely to be easier than apheresis which requires 4 hour session every week/2 weeks in hospital. Evinacumab is a 1 hour infusion monthly and could potentially be delivered at home. Many patients cannot tolerate the procedure because of side effects, challenges with vascular access, existing atherosclerotic cardiovascular disease and cardiac valve disease.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Lomitapide is an oral therapy but is not well tolerated (severe burden from diet restriction, gastrointestinal and hepatic side effects) by a proportion of patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Start rules should include diagnosis of homozygous FH and LDL-c not at target. Stop rules could be not achieving a LDL-c reduction >15%.
15. 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?	If a patient no longer requires apheresis, then the weekly hospital visits, missed work/education and psychological benefits need to be factored in.
16. 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?	Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits? Definitely. How might it improve the way that current need is met?

	It gives a third tool to be employed in lowering LDL in these very high risk patients, particularly where apheresis +/- Lomitapide have not been sufficient at brining LDL-c to target.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, bringing LCL-c to target to lower risk of CHD and other atherosclerotic disease, cardiac valve disease and aortic root disease
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No real side effects documents from trials thus far

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, LDL-c. Ideally CV outcomes, but this would be impossible given rarity of the condition.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
18d. 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 treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
21. How do data on real-world experience compare with the trial data?	No real world data available as yet

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• It gives a third tool to be employed in lowering LDL in these very high risk patients, particularly where apheresis +/- Lomitapide have not been sufficient at brining LDL-c to target. • Little known side effects, the current treatments come with side effect some can be severe along with significant dietary restrictions. • Potentially to free a patient from apheresis and having to miss work / education. • Once established, potentially can be treated at home. • The trials show a 40-50% reduction in LDL-c which translates to very large clinical impact. This reduction in LDL-C is very important to avoid future complications like CHD, other ASCVD like PVD, aortic valve disease and aortic root disease, even more than what is expected for general population as the only risk factor for ASCVD in these patients is very high cholesterol.

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BMJ TAG

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

STA Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Mariana Bacelar	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report.
Vicky Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Nicole Downes	Critical appraisal of the company's submission and critical appraisal of the clinical evidence
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

AE	Adverse event
ANGPTL3	Angiopoietin-like protein 3
Apo	Apolipoprotein [type]
BMI	Body mass index
CEM	Cost-effectiveness model
CHD	Coronary heart disease
CI	Confidence interval
CTT	Cholesterol Treatment Trialists'
CV	Cardiovascular
CVD	Cardiovascular disease
CSR	Clinical study report
DBTP	Double-blind treatment period
EAG	External Assessment Group
EAS	European Atherosclerosis Society
FDA	Food and Drug Administration
EMA	European Medicines Agency
FH	Familial hypercholesterolaemia
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HoFH	Homozygous familial hypercholesterolemia
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
KM	Kaplan-Meier
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LDRAP1	Low-density lipoprotein receptor adaptor protein 1
LPL	Lipoprotein lipase
LLT	Lipid lowering therapy
LOF	Loss of function
LOCF	Last observation carried forward
LS	Least squares
MACE	Major adverse cardiovascular event
MAIC	Matching-adjusted indirect comparison
MI	Myocardial infarction
MR	Magnetic resonance
MTP	Microsomal triglyceride transfer protein

Nab	Neutralising antibody
NICE	National Institute of Health and Care Excellence
OLTP	Open label treatment period
OWSA	One-way sensitivity analysis
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
PLD	Patient level data
QALY	Quality-adjusted life year
QoL	Quality of life
SA	Stable angina
SAE	Serious adverse event
SF-36	Short Form 36
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TIA	Transient ischaemic attack
TC	Total cholesterol
TG	Triglycerides
UA	Unstable angina
VEGF	Vascular endothelial growth factor
VLD-C	Very low-density lipoprotein cholesterol

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs; Section 1.4).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

The EAG notes that the company considers evinacumab to primarily replace the use of lomitapide in the current treatment pathway and the MHRA marketing authorisation is for its use as an adjunct to diet and other LDL-C lowering therapies. The EAG considers that based on the company's restricted positioning of evinacumab as a replacement for lomitapide, evinacumab should be given after LDL apheresis in the treatment pathway. The EAG has therefore focussed its critique and analysis of the clinical and cost-effectiveness of evinacumab based on this positioning of evinacumab in the treatment pathway (i.e. after maximally tolerated background lipid lowering therapies and LDL apheresis [excluding lomitapide]).

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Omission of continuation of background LLT as a comparator.	Table 2 and Section 2.3.3
2	Uncertainty in the results of the matching adjusted indirect comparison for evinacumab versus lomitapide.	Table 3 and Section 3.4
3	Omission of cost-effectiveness analysis in adolescent population.	Table 4 and Section 2.3.1
4	The model does not fully capture the health outcomes associated with secondary prevention patients.	Table 5 and Section 4.2.3
5	CVM from Thompson *et al*. may not be generalisable to UK HoFH patients.	Table 6 and Section 4.2.6
6	Baseline LDL-C used in the model.	Table 7 and Section 4.2.7.1

Abbreviations CV, cardiovascular; CVM, cardiovascular mortality; EAG, External Assessment Group; LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering therapy.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are that the EAG prefers the use of the ELIPSE baseline characteristics and background

treatments in the model without further adjustments; the inclusion of secondary prevention patients and slight changes to the costs and health state utilities considered. Furthermore, the EAG considers that background LLT should also be considered as a comparator in the economic analysis.

1.2 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.

Overall, the technology affects QALYs and costs by reducing the risk of fatal and non-fatal CV events by lowering a patient's low-density lipoprotein-cholesterol (LDL-C) concentration. As CV risk decreases, patients are more likely to remain alive and in health states associated with a higher health related quality of life (HRQoL) and lower costs, leading to QALY and cost savings.

The key parameters driving the cost-effectiveness results are the source used for the relative treatment effect used for lomitapide vs evinacumab, the inclusion of background LLT as a comparator to evinacumab in the model and treatment acquisition costs.

1.3 Summary of the EAG's key issues

Table 2. Issue 1: Omission of continuation of background LLT as a comparator.

Report section	2.3.3
Description of issue and why the EAG has identified it as important	The EAG is concerned with the company's positioning of evinacumab as a replacement for lomitapide as this could be a larger population than those currently receiving lomitapide. That is, the population where clinicians would want to use lomitapide is likely to be larger than the population that receives lomitapide, principally due to toxicity issues. In those patients that clinicians would want to use lomitapide but cannot, the EAG considers that they would receive continued use of LLTs (with or without LDL apheresis). The EAG therefore considers that while lomitapide (with or without LDL apheresis) is a key comparator for the adult population, continuation of background LLTs (without lomitapide) is also a relevant comparator for those patients unsuitable for lomitapide. In addition, the EAG considers that continuation of maximally tolerated background non-lomitapide LLTs is potentially the main comparator for evinacumab in the adolescent population based on the company's proposed positioning for evinacumab. Additionally, the EAG considers that based on the company's restricted positioning of evinacumab as a replacement for lomitapide, evinacumab should be given after LDL apheresis in the treatment pathway.
What alternative approach has the EAG suggested?	The inclusion of continuation of background LLT (with or without LDL apheresis) as a comparator for both the adolescent and adult populations using the trial results from the DBTP of ELIPSE.

What is the expected effect on the cost-effectiveness estimates?	The EAG has provided an EAG base case cost-effectiveness analysis comparing evinacumab to the continuation of background LLT (with LDL apheresis). In the analysis evinacumab is shown to generate additional costs and QALYs compared to continuation of background LLTs, leading to an ICER of £3,336,965 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Additional analyses of cost-effectiveness excluding patients on background lomitapide from both treatment arms of ELIPSE to align the clinical data with the company's positioning of evinacumab as a replacement for lomitapide, although the EAG acknowledges that this would break randomisation.

Abbreviations: DBTP, double-blind treatment-period; EAG, External Assessment Group, HoFH, homozygous familial hypercholesterolaemia; LDL, low-density lipoprotein; LLT, lipid lowering therapy.

Table 3. Issue 2: Uncertainty in the results of the matching adjusted indirect comparison for evinacumab versus lomitapide.

Report section	3.4
Description of issue and why the EAG has identified it as important	The EAG considers the results of the company's MAIC comparing evinacumab with lomitapide to be uncertain, principally due to poor matching between the studies, which is exacerbated by the limited reporting of baseline characteritsics from Cuchel *et al*. 2013 and the small number of patients included in each study. The EAG considers the main MAIC analyses with adjustment for all variables to be the most suitable for decision making and therefore focuses on these results but is concerned by the resulting low ESSs. In addition, the EAG is concerned that in the MAIC used in the company's base case, the evinacumab data are confounded by the inclusion of patients who were on background lomitapide in ELIPSE (25.6% of patients in the evinacumab arm). The EAG also notes that in the MAIC excluding the patients on lomitapide in the evinacumab arm of ELIPSE, the ESS for the main analysis, when all the matching variables were applied, decreased from 9.9 to 3.9. The EAG therefore considers the results from the MAICs to be uncertain but considers the MAIC excluding the patients on lomitapide in the evinacumab arm of ELIPSE to be more consistent with the company's positioning of evinacumab in the treatment pathway.
What alternative approach has the EAG suggested?	The EAG has conducted two additional scenarios comparing evinacumab to lomitapide: 1) the EAG used the MAIC results excluding lomitapide from the evinacumab arm; and 2) due to the uncertainty in the different MAICs conducted, the EAG considers that there is no robust evidence to indicate that evinacumab is more or less effective than lomitapide. As such the EAG has conducted an exploratory cost-minimisation analysis assuming equivalent efficacy between evinacumab and lomitapide.
What is the expected effect on the cost-effectiveness estimates?	The results of the EAG's analysis using the MAIC excluding lomitapide from the evinacumab arm led to an ICER of £25,193,589 in the south-western quadrant of the cost-effectiveness plane, meaning that lomitapide is more effective and more costly than evinacumab. The results of the cost minimisation analysis indicate that evinacumab is cost-saving compared to lomitapide.
What additional evidence or analyses might help to	Additional analyses of cost-effectiveness as detailed above. Furthermore, the EAG considers this issue likely to be unresolvable based

resolve this key issue?	on the clinical evidence available at this time for evinacumab and lomitapide; the EAG considers that data from an adequately powered head-to-head RCT of evinacumab versus lomitapide is required.

Abbreviations: EAG, External Assessment Group, MAIC, matching-adjusted indirect comparison; RCT, randomised controlled trial.

Table 4. Issue 3: Omission of cost-effectiveness analysis in adolescent population.

Report section	2.3.1
Description of issue and why the EAG has identified it as important	The EAG notes that there is no assessment of the cost-effectiveness of evinacumab in adolescents with HoFH presented in the CS and that the company does not provide a rationale for why this population has not been considered separately to the adult population. The EAG considers this to be of particular importance as the comparator used in the company's analyses of cost-effectiveness utilise data for the comparator drug lomitapide which is not a treatment option in the adolescent population.
What alternative approach has the EAG suggested?	The EAG considers the company should present an analysis of cost-effectiveness using data for a relevant comparator for the adolescent HoFH population. The EAG considers continued background LLT (with or without LDL apheresis) to be the primary comparator for the adolescent population as detailed in Issue 1 above. [redacted] in the adolescent population with appropriately adjusted baseline characteristics and inputs for an adolescent population in the economic model.
What is the expected effect on the cost-effectiveness estimates?	The EAG has provided an EAG base case cost-effectiveness analysis comparing evinacumab to the continuation of background LLTs (with LDL apheresis) in an adult population. In the analysis evinacumab is shown to generate additional costs and QALYs comparatively to continuation of background LLTs, leading to an ICER of £3,336,965 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers an analysis of cost-effectiveness using data for relevant comparator(s) for the adolescent HoFH population is required. In addition, data from the final analysis of the adolescent subgroup in the long-term, open-label, single-arm study of evinacumab: Study R1500-CL-1719 would be beneficial to confirm the long-term efficacy of evinacumab in this subgroup.

Abbreviations: CS, company submission; EAG, External Assessment Group, HoFH, homozygous familial hypercholesterolaemia; LDL, low-density lipoprotein; LLT, lipid lowering therapy.

Table 5. Issue 4: The model does not fully capture the health outcomes associated with secondary prevention patients.

Report section	4.2.3
Description of issue and why the EAG has identified it as important	The EAG considers that the model developed by the company lacks the functionality to distinguish between primary and secondary prevention patients. Given the distinct difference in acute and post-event health state utilities between primary and secondary events, as per Ara and Brazier, the

	model therefore fails to capture the full health outcomes associated with HoFH. As the majority of the ELIPSE patient cohort included secondary prevention patients and the EAG's clinical experts outlined that in UK clinical practice approximately 70% of patients are secondary prevention patients by 42 years old, the EAG considers it is crucial that model captures the currently unaccounted costs and health outcomes differences associated with suffering from primary and secondary CV events.
What alternative approach has the EAG suggested?	At clarification the EAG requested that the company considered a secondary prevention population in the model, with respective HRQoL and cost differences between primary and secondary CV events. The company conducted a scenario assuming 50% of patients in the model were secondary prevention patients but failed to capture the impact on patients' quality of life and costs appropriately.
What is the expected effect on the cost-effectiveness estimates?	It is difficult to anticipate the full extent of the impact of appropriately accounting for the trajectory of secondary prevention patients (and respective outcomes) over the model lifetime. Nonetheless, the EAG notes that the drop in patients' utility, both for the acute event period and the post-acute event, from baseline would be higher if the company had more appropriately captured the change in patients' utility as suggested by the EAG.
What additional evidence or analyses might help to resolve this key issue?	The company should amend the model as previously suggested by the EAG.

Abbreviations: EAG, External Assessment Group; HoFH, homozygous familial hypercholesterolaemia; HRQoL, health related quality of life; QALYs, quality adjusted life years.

Table 6. Issue 5: Cardiovascular mortality from Thompson *et al.* may not be generalisable to UK HoFH patients.

Report section	4.2.64.2.6
Description of issue and why the EAG has identified it as important	The study by Thompson *et al*. was chosen by the company to inform CVM risk in the model as the patient study cohort was deemed representative of UK HoFH patients' CV risk, patient characteristics, background treatment mix and baseline LDL-C values.[1] While the study is specific to UK HoFH patients and is therefore preferable to using general population estimates, the EAG considers the study is not representative of UK HoFH patients' CVM risk, currently used background treatments or baseline LDL-C values. With respect to CVM risk, the authors of the Thompson study comment how patients who died in the study were distinctly different to those alive with this difference being driven by the access to treatments such as statins, which were only granted marketing authorisation in the UK four years before the average year of death of the patients who died. The EAG considers that the inclusion of this less well treated group who do not reflect current UK clinical practice likely leads to an overestimation of CVM in the model. In addition to those who died in the study having limited access to statins, no

	patients were treated with evolocumab given it was only granted marketing authorisation in the UK in 2015. Finally, advances in the LDL apheresis techniques also resulted in apheresis being performed more frequently and efficiently for patients alive by the end of the study. Therefore, the EAG considers the study is not fully representative of current background LLT treatments in the NHS. Additionally, as CVM from Thompson was used to derive the transition probabilities for non-fatal CV events from fatal CV events, all transition probabilities in the model are likely to be overestimated.
What alternative approach has the EAG suggested?	The EAG has suggested that the company conducts additional sensitivity analyses around model CVM, using alternative lower risks.
What is the expected effect on the cost-effectiveness estimates?	The EAG expects the total modelled QALYs would be higher had a more reflective CVM risk of the HoFH population been included in the model and the incremental difference in QALYS would be greater as the more effective treatment leads to greater reductions in CVM.
What additional evidence or analyses might help to resolve this key issue?	Either using CVM from a more representative group of HoFH patients or providing sufficient evidence to validate that the CVM from Thompson is similar to that observed in a population more representative of the UK HoFH population.

Abbreviations: EAG, External Assessment Group; CV, cardiovascular; CVM, cardiovascular mortality; LDL-C, low-density lipoprotein-cholesterol.

Table 7. Issue 6: Baseline LDL-C used in the model.

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	The EAG considers that the methodology employed by the company to estimate baseline LDL-C in the model lacks validity and is not methodologically robust. The company informed baseline LDL-C in the model by using the Thompson *et al.* study, and then adjusting the latter to the difference in background LTT treatments used in ELIPSE, which the EAG considers more representative of current clinical practice. The baseline LDL-C from the Thompson study was calculated at 8.7 mmol/L, compared to 6.7 mmol/L in ELIPSE patients, who were treated with a more reflective mix of background LLT treatments. Therefore, the EAG considers that baseline LDL-C from the Thompson study is not representative of UK HoFH patients. The company's methodology overestimates baseline LDL-C and therefore the reduction in LDL-C from treatments when compared to ELIPSE.
What alternative approach has the EAG suggested?	The EAG suggested that no adjustments were needed when using the baseline LDL-C from ELIPSE in the model. Furthermore, the relative treatment effects calculated from the MAIC could be directly applied to the baseline LDL-C measured from ELIPSE which already accounted for the LLT background treatment effects in the study.
What is the expected effect on the cost-effectiveness estimates?	The EAG expects that as baseline LDL-C and therefore reductions in LDL-C are overestimated in the model, leading to the incremental difference in costs and QALYs potentially being overestimated between treatments.

What additional evidence or analyses might help to resolve this key issue?	As the Thompson study population is not representative of current UK HoFH patients the EAG considers that no additional evidence for the methodology employed by the company would resolve the issue.

Abbreviations: EAG, External Assessment Group

1.4 Summary of EAG's preferred assumptions and resulting ICER

Table 8. Summary of EAG's preferred assumptions and resulting ICER

Scenario	Incremental costs	Incremental QALYs	ICER
Company corrected base case (post clarification)	[redacted]	[redacted]	Dominant
Using baseline LDL-C from ELIPSE and	[redacted]	[redacted]	Dominant
Using the MAIC treatment effects with lomitapide patients excluded from the evinacumab arm	[redacted]	[redacted]	£24,322,725 (SW)
Assuming 30% of patients are primary prevention patients and 70% are secondary prevention patients	[redacted]	[redacted]	Dominant
TA694 preferred utility values for MI (0.721) and post-TIA (0.78) to inform the utility multipliers for those health states	[redacted]	[redacted]	Dominant
Annual LDL-apheresis disutility of -0.205	[redacted]	[redacted]	Dominant
Four vials per evinacumab administration	[redacted]	[redacted]	Dominant
Evinacumab administration cost scenario (£621 for the first year, £552 for subsequent years).	[redacted]	[redacted]	Dominant
LDL-apheresis discontinuation rate of 16.67%	[redacted]	[redacted]	Dominant
EAG's preferred monitoring costs based on clinical expert monitoring resource use assumptions and including SmPC monitoring recommendations for lomitapide	[redacted]	[redacted]	Dominant
EAG preferred health state costs	[redacted]	[redacted]	Dominant

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.3.

As the EAG considers that the MAIC excluding the patients on lomitapide in the evinacumab arm of ELIPSE to be more consistent with the company's positioning of evinacumab in the treatment pathway and that LLTs are an additional comparator of interest, the EAG has provided two base cases (Table 9 and Table 10).

Table 9. Evinacumab and lomitapide cost effectiveness analysis using the MAIC treatment effects with lomitapide treated patients excluded in evinacumab arm

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Lomitapide	5,700,073	12.20	8.73	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,193,589 (SW)

Abbreviations: ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality adjusted life year; SW, south-west quadrant ICER.

Table 10. Evinacumab and SoC LLTs cost effectiveness analysis using ELIPSE treatment effects & EAG assumptions

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
LLTs	262,092	11.16	7.98	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3,336,965

Abbreviations: ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality adjusted life year.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost effectiveness of evinacumab-dgnb (EVKEEZA®; Ultragenyx), hereafter referred to as evinacumab, for treating homozygous familial hypercholesterolaemia (HoFH) in people aged 12 years and over. In the company submission (CS), the company reports that they are positioning evinacumab primarily as a replacement for lomitapide in the current treatment pathway and that evinacumab would be an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies. The company considers lomitapide to be a third-line treatment for adults and states that there are no third-line treatment options currently available in United Kingdom (UK) clinical practice for HoFH patients aged 12 to 17 years old (adolescents). The external assessment group (EAG) notes that there is no assessment of the cost-effectiveness of evinacumab in adolescents presented in the CS. The EAG's critique of the population and company's choice of comparators is detailed in Section 2.3.

2.2 Background

Within Section B.1 of the CS, the company provides an overview of HoFH that includes:

- the aetiology and pathophysiology of HoFH;
- the diagnosis of HoFH;
- the prevalence of HoFH;
- disease progression and prognosis of HoFH;
- patient burden and impact on health-related quality of life (HRQL); and
- treatments options for HoFH.

HoFH is a rare autosomal dominant genetic disorder of lipid metabolism that results in severely elevated plasma total cholesterol and LDL-C levels.[2, 3] The high cholesterol in HoFH patients can lead to the premature formation of atherosclerotic plaques in arteries in the body and this significantly increases the risk of premature cardiovascular disease and death.[4]

Patients with HoFH have functional mutations in genes such as low-density lipoprotein receptor (LDLR), apolipoprotein B (ApoB), proprotein convertase subtilisin/kexin type 9 (PCSK9), and people with HoFH can be classified into three categories: true homozygotes, compound heterozygotes, and double heterozygotes.[5, 6] True homozygotes carry the same mutation on both alleles of the affected

gene, whereas compound heterozygotes carry a different mutation on each allele of the affected gene, and double heterozygotes carry a mutation on two different genes. HoFH can be further classified based on the extent of the impact of mutations on LDLR functionality. Patients classed as LDLR-deficient ("null-null") have little to no low-density lipoprotein (LDL) binding and uptake activity, which results in more severe disease than those with higher levels of LDLR activity.

The EAG notes that in 2018, it was estimated that the prevalence of HoFH may be 1 in 670,000 adults in England, with around 1 new case of HoFH being diagnosed every year.[7] Additionally, based on these prevalence rates, it is estimated that there are between 43 and 66 adult patients in England with HoFH (calculated in the lomitapide clinical commissioning policy using Office for National Statistics [ONS] 2016 data).[7] The EAG notes that this estimate does not include adolescents and that evinacumab is a treatment indicated for people aged 12 years and over.

The current treatment options for reducing LDL-C in patients with HoFH in the UK include: diet and lifestyle modifications, statins (usually high-intensity), ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inhibitors) such as evolocumab, lomitapide, and LDL apheresis. In general, HoFH patients will require a combination of treatments with doses and treatment regimens tailored to the individual patient and not all HoFH patients will reach their target LDL-C with the currently available treatments. In some patients, liver transplantation may be considered but the EAG's clinical experts report that this is not a commonly used treatment option. The EAG notes that evinacumab would potentially provide a new treatment option with a novel mechanism of action (inhibition of angiopoietin-like protein 3 [ANGPTL3]) for patients with HoFH.

2.2.1 Treatment pathway

The EAG's clinical experts reported that there is no specific standard UK guideline for the treatment of HoFH patients, although there is a National Institute for Health and Care Excellence (NICE) clinical guideline: 'Familial hypercholesterolaemia: identification and management', that provides general guidance on treatment of HoFH.[8] The EAG also notes that the 2016 HEART UK statement on the management of HoFH in the UK provides consensus statements for the management of HoFH.[5]

The company highlighted the presence of the European Atherosclerosis Society (EAS) consensus guidelines for the treatment of HoFH, published in 2014[6] and updated in May 2023.[9] The EAG notes that the positioning of LDL apheresis in the EAS consensus guidelines treatment pathway has changed – in 2014 it was recommended to be considered at the start of the treatment pathway, whereas in the 2023 update it has been moved to later in the treatment pathway. The EAG also

notes that the 2023 EAS guidelines include ANGPTL3 directed therapy (e.g. evinacumab) as an alternative to lomitapide.

The company's summary of the current treatment pathway and their proposed positioning of evinacumab is provided in Figure 1. The EAG's clinical experts were generally in agreement with the company's outline of the current treatment pathway and reported that the drugs are additive with discontinuation of earlier drugs in the treatment pathway only considered if there is intolerance or where they are deemed to be ineffective in reducing LDL-C. The EAG's clinical experts agreed with the company that the PCSK9 inhibitors such as evolocumab are generally ineffective in people with mutations affecting the PCSK9 gene, or people with null/null LDLR mutations.

The EAG notes that in Figure 1, the company's proposed positioning of evinacumab is at third-line, following evolocumab and/or LDL apheresis. The company also confirmed in their response to clarification questions that they consider evinacumab to be an alternative treatment option to lomitapide and they do not consider LDL apheresis to be a comparator. The EAG notes from its clinical experts that LDL apheresis is an invasive procedure requiring a minimum of weekly attendance at specialist centres for treatments and thus it is generally used after failure to reach target LDL-C on the other available LLTs. However, the EAG is unclear what proportion of UK HoFH patients are currently receiving LDL apheresis and also considers it likely that not all patients potentially eligible for evinacumab will be on LDL apheresis.

The EAG notes that the NHS commissioning policy for lomitapide requires all clinically indicated existing treatments in the treatment pathway, including LDL apheresis, to be given prior to commencement of lomitapide (Box 1). In addition, it should be noted that lomitapide does not have a marketing authorisation in England for use in adolescents and the EAG's clinical experts agreed that lomitapide is only used in adults.

Box 1: Summary of NHS England 2018 Clinical Commissioning Policy: Lomitapide for treating homozygous familial hypercholesterolaemia (adults)[7]

Lomitapide will be routinely commissioned when the following criteria are met:

- Lomitapide should only be considered when HoFH is not adequately controlled by existing treatments and people are at high risk of cardiovascular events:
    - Existing treatments: These should include ALL of the treatments most commonly used from baseline to week 26 in the main trial, as long as they are clinically indicated: statins, ezetimibe, bowel assisted sequestrants and apheresis (can be combined as appropriate). In addition, evolocumab if HoFH is LDLR defective or unknown.

- HoFH that is not adequately controlled and at high risk of cardiovascular events: where LDL-C is as follows (based on specific therapeutic targets for LDL-C lowering in HoFH set by HEART UK (France et al. 2016) and the European Atherosclerosis Society)
  - >2.5mmol/L for adults with FH
  - >1.8mmol/L for adults with atherosclerotic cardiovascular disease.

AND

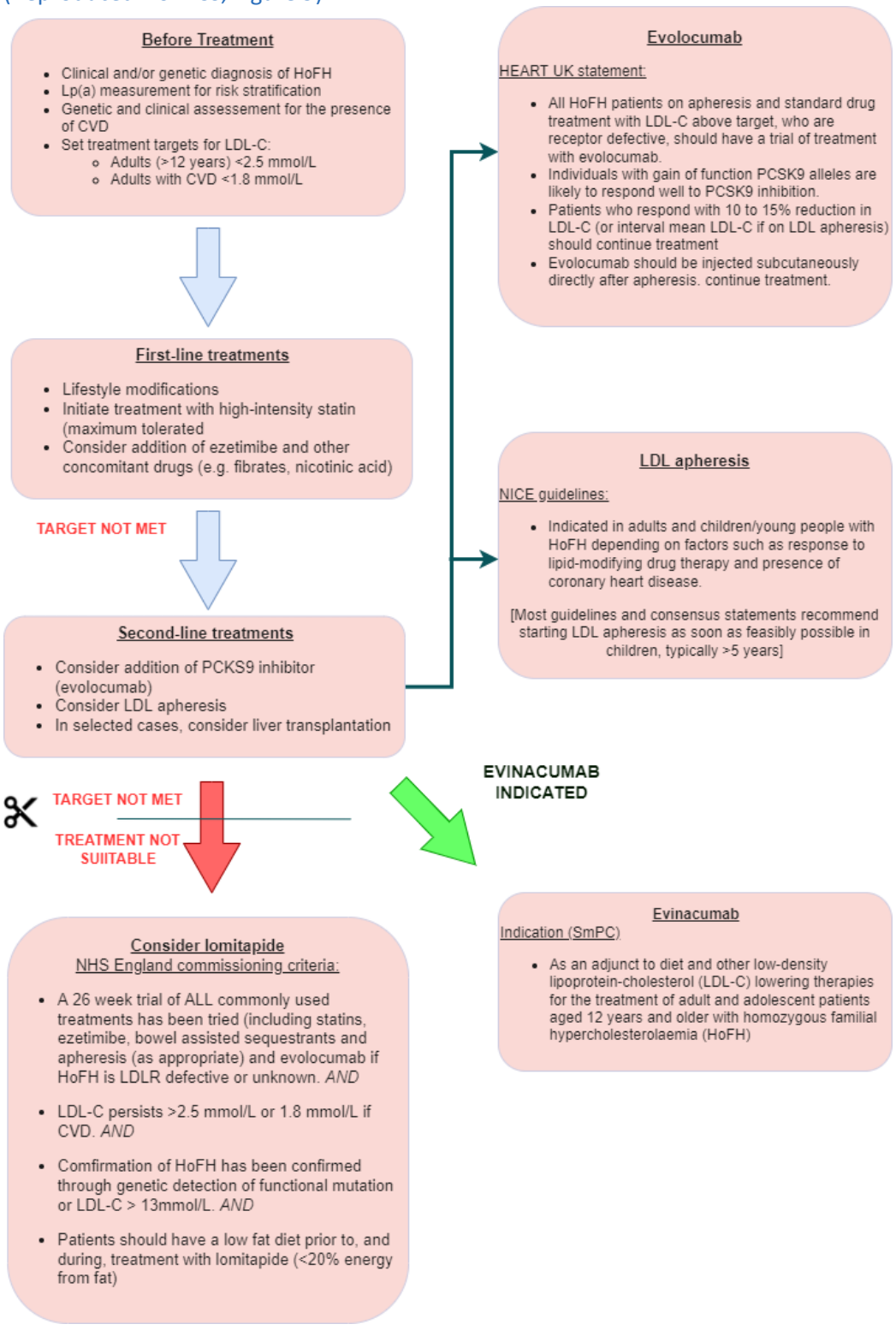
- Confirmation of HoFH should be obtained using 1 of the following criteria:
  - Documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality, OR;
  - Untreated LDL-C greater than 13 mmol/L

AND

- Patients should have a low fat diet prior to, and during, treatment with lomitapide (<20% energy from fat).

The company also confirmed in their response to clarification questions that in the treatment pathway for the adolescent population, evinacumab is expected to be used, "*the same as for adults, although it is noted that lomitapide is not a treatment option for this cohort*". The company did not specify any comparators for evinacumab in the adolescent population and clinical data for adolescents in the CS is limited to only a small number of patients with the evinacumab patients mainly from a single-arm study (R1500-CL-1719; n=[redacted])[10]. In addition, the company does not provide a cost-effectiveness analysis of evinacumab in the adolescent population. The EAG considers it important to highlight that the cost-effectiveness results for evinacumab versus lomitapide presented by the company are only relevant to the adult population as lomitapide is not a relevant comparator in the adolescent population. For the EAG critique of the company's choice of comparators see Section 2.3.3.

Figure 1. Company's UK treatment algorithm for management of HoFH derived from several sources (Reproduced from CS, Figure 9)



Abbreviations: CVD, cardiovascular disease; EAS, European Atherosclerosis Society; FH, familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; PCSK9; proprotein convertase subtilisin/kexin type 9; SmPC, summary of product characteristics.

Derived from guidelines and consensus statements including NICE[8], NHS England[7], HEART UK[11] and EAS[6].

2.3 Critique of the company's definition of the decision problem

A summary of the final scope issued by NICE,[12] together with the company's rationale for any deviation from this, is provided in Table 11. Key differences between the decision problem addressed in the CS and the scope are discussed in greater detail in the sections that follow below. The EAG considers the main differences between the decision problem specified by the company and the NICE final scope are that the company has focused on lomitapide as the comparator in the adult population, and that there is an absence of a cost-effectiveness analysis for evinacumab in the adolescent population (people aged 12 to 17 years).

Table 11. Summary of decision problem (Adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	People with homozygous familial hypercholesterolaemia aged 12 years and over	Unchanged	N/A	The EAG notes that only 2 patients aged between 12 and 17 years (adolescents) were enrolled in ELIPSE[13] and that some patients in the trial were diagnosed with HoFH based on clinical criteria rather than genetic criteria. The EAG's clinical experts reported that the baseline characteristics of patients in the ELIPSE RCT are broadly consistent with patients with HoFH in the UK population, although the background LLTs may be slightly different. The EAG is concerned that there is limited clinical data for evinacumab versus the comparators in the adolescent subgroup, although there are additional single-arm trial data for evinacumab. See Section 2.3.1 below for further discussion.
Intervention	Evinacumab as an adjunct to diet and other LDL-C lowering therapies	Unchanged	N/A	The treatment regimen for evinacumab in the ELIPSE RCT is consistent with the MHRA marketing authorisation for evinacumab, although the EAG's clinical experts reported that the background LLTs in the trial may differ to the LLTs used in the UK HoFH population. See Section 2.3.2 below for further discussion.

Comparator(s)	**For people aged 18-years and older:** Established clinical management without evinacumab (including but not limited to statins, diet and lifestyle changes, ezetimibe, lomitapide, evolocumab and LDL apheresis) **For people aged 12-17:** Established clinical management without evinacumab (including but not limited to statins, diet and lifestyle changes, ezetimibe, evolocumab and LDL apheresis)	**For people aged 18-years and older:** Lomitapide **For people aged 12-17:** No comparator is considered	The company believes the current comparator does not accurately describe the decision problem, as it implies that evinacumab is intended for use as an addition to lomitapide, whereas in fact evinacumab is primarily intended to *replace the use of lomitapide*. **For people aged 18 years and older**, lomitapide is currently positioned as a third-line treatment by 2014 EAS consensus guidelines (after statins, ezetimibe, PCSK9 inhibitors where indicated, LDL apheresis where indicated) [6]. The NHS England commissioning policy document places lomitapide in the same position of the pathway [7], with lomitapide recommended for use in this context. The most recent EAS consensus statement (published 2023) recommends lomitapide and/or evinacumab with or without LDL apheresis as third-line treatment.[9] There are no robust data published on the combined use of lomitapide and evinacumab. Whilst there are no known negative drug-drug interactions associated with the concomitant use, both drugs having different mechanisms of action would likely have an additive effect [13]. It is expected however that the combination of treatments would not be offered on the NHS as it would be prohibitively expensive. Lomitapide is also associated with numerous very common GI	The EAG notes that the company considers lomitapide to be the only comparator for people aged 18 years and older and that no comparators are explicitly specified by the company for people aged 12 to 17 years. The final scope issued by NICE included established clinical management without evinacumab as a comparator for both populations and the EAG's clinical experts reported that not all patients would receive lomitapide in clinical practice. The EAG is therefore concerned that the company has not considered treatments for patients not on lomitapide. The EAG considers that established clinical management without evinacumab or lomitapide (continuation of background LLT with or without LDL apheresis) should be considered a comparator for both people aged 18 years or over and people aged 12 to 17 years. In addition, the EAG considers the commencement of LDL apheresis (with continuation of background LLT) at third-line to be a potential comparator for both populations based on the 2023 EAS guidelines but notes the company's restricted positioning of evinacumab as a replacement for lomitapide. See Section 2.3.3 below for further discussion.

			and common hepatic AEs and tolerability issues that are not reported for evinacumab Lomitapide is also associated with AEs and tolerability issues [14] that are not experienced with evinacumab [15]. The company contends that evinacumab should therefore be a replacement for, rather than an addition to, lomitapide in adults for the reasons discussed in this submission document. **For people aged between 12 and 17 years**, evinacumab is indicated, in contrast to lomitapide which is not indicated in this population. However, there are only very limited comparative evidence for this group (2 subjects enrolled in the ELIPSE trial were in this age range), with most evidence being limited to single-armed data only. For this reason, the use of evinacumab in this age group will be considered in the clinical effectiveness element of the submission (where there is a significant unmet need in this population), but will not be considered in the cost-effectiveness analysis.	
Outcomes	The outcome measures to be considered include: plasma lipid and lipoprotein levels, including LDL-C, non-HDL cholesterol, apolipoprotein B and lipoprotein a	Unchanged	N/A	The outcomes reported in the ELIPSE trial are mostly reflective of those specified in the NICE final scope and the EAG's clinical experts reported that the primary outcome, reduction of LDL-C, is the key clinical outcome of interest in the treatment of HoFH. Additionally the EAG notes the only clinical outcome from the trial used by the company was evinacumab LDL-C reduction, which was used to inform the

	requirement of procedures including LDL apheresis and revascularisation fatal and non-fatal cardiovascular events mortality adverse effects of treatment health-related quality of life.			MAIC where ELISPE patients were matched to those of the lomitapide study by Cuchel *et al.* [16] The EAG notes that there are no data reported on revascularisation events in ELIPSE and that data on fatal and non-fatal cardiovascular events are limited to the data reported as adverse events as these were not specified as efficacy outcomes in the trial.
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. 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	The economic analysis is fully consistent with the NICE reference case	N/A	The EAG notes that the time horizon was appropriate, and costs considered were from an NHS and Personal Social Services perspective. Cost effectiveness results were also expressed in terms of cost per quality adjusted life year.

	technologies will be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: People aged 12 to 17 years inclusive Presence or level of risk of cardiovascular disease Mutational status (e.g., LDLR status, compound heterozygotes, double heterozygotes)	Only analysis on the clinical effectiveness (and safety) of evinacumab in these subgroups will be undertaken.	**People aged 12 to 17 years inclusive:** there are only very limited comparative evidence in this subgroup which is insufficient to allow for robust cost effectiveness analysis. **Presence or level of risk of cardiovascular disease**: all patients with HoFH are considered to be at high risk of cardiovascular disease. Management is determined by target drug commencement and titration to achieve LDL-C levels, not overall assessment of cardiovascular risk. **Mutational status (e.g., LDLR status, compound heterozygotes, double heterozygotes)**: evinacumab is effective in all patients with HoFH, regardless of the underlying genetic mutation. This is also true for lomitapide. However, this is not true for all background treatments.	The company has presented subgroup results for the primary outcome in ELIPSE (mean change in LDL-C from baseline to Week 24) for the adolescent and mutational status subgroups. In addition, results for [redacted] are provided for the adolescent subgroup from the single-arm study R1500-CL-1719.[10] The EAG notes that the company has not presented subgroup results based on presence or level of cardiovascular (CV) disease and considers all patients to be at high-risk of CV disease. Additionally, the EAG notes that 90.8% of patients in ELIPSE had a history of CV disease or CV risk factors at baseline and there is baseline data in ELIPSE by pre-existing cardiovascular disease and risk factors but no prespecified subgroup analyses for these characteristics. The EAG's clinical experts reported that they would not expect CV risk to be a treatment effect modifier for evinacumab.
Special considerations, including issues related to equity or equality	None listed in the final scope.	The use of evinacumab in people aged 12 to 17 years (inclusive) raises potential equity issues.	As noted, lomitapide, the only other effective pharmacological treatment available as third-line treatment, is not indicated in this age group. Thus, there is currently an unmet need in this age group that needs to be addressed. Age is a protected characteristic.[17]	The EAG notes that there were no special considerations listed in the NICE final scope but the company considered age important due to the age restriction for the use of lomitapide.

Abbreviations: CV, cardiovascular; EAG, External Assessment Group; HoFH, homozygous familial hypercholesterolaemia; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LLT, lipid lowering therapy; MAIC, matching-adjusted indirect comparison; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; RCT, randomised controlled trial.

2.3.1 Population

The ELIPSE trial (study R1500-CL-1629)[13] was a 24 week multicentre phase 3, double-blind, parallel-group randomised controlled study of evinacumab versus placebo in patients aged 12 years and over with HoFH and stable background lipid lowering therapy (LLT) and a stable LDL apheresis schedule (if applicable). The study had an 8-week run-in period for patients who did not have a functional diagnosis of HoFH and opted to undergo genotyping for confirmation, or whose background medical LLT or LDL apheresis schedules were not stable prior to the 2-week screening period. In addition, there was a 24 week open label treatment period with evinacumab following the double-blind treatment period.

The EAG notes that the ELIPSE study used a 2:1 randomisation schedule and thus there is a smaller group of patients in the placebo arm. Additionally, the EAG notes that only 2 patients aged between 12 and 17 years ([adolescents] one in each study arm) were enrolled in ELIPSE. The company does not present a cost-effectiveness analysis for the adolescent population in the CS but does present additional clinical data from an interim analysis of the single-arm long-term safety and efficacy study (R1500-CL-1719);[10] Study R1500-CL-1719 enrolled [redacted]

The EAG notes that 32% of patients in ELIPSE had a clinical diagnosis of HoFH rather than a genetic diagnosis and the EAG's clinical experts reported that patients in the UK would generally be expected to have a genetic diagnosis. However, the EAG's clinical experts also reported that the clinical criteria used to diagnose HoFH in ELIPSE appear comprehensive and likely to capture patient's representative of those with HoFH in UK clinical practice.

In the ELIPSE trial, patients in both the evinacumab and placebo arms continued treatment with their background LLTs and LDL apheresis, and the background LLTs and LDL apheresis schedules were required to be stable prior to commencement of the double-blind treatment period.

Based on clinical expert advice, the EAG considers that the baseline characteristics of patients in the ELIPSE trial are broadly consistent with the HoFH patients seen in UK clinical practice with the exception of the background LLTs and LDL apheresis usage; the EAG's clinical experts reported that statin (93.8% in ELIPSE) and ezetimibe (75.4%) usage maybe higher in the UK. In addition, the EAG notes that background LLTs in ELIPSE included lomitapide and that ELIPSE thus differs to the

company's proposed positioning of evinacumab as a replacement for lomitapide in the UK treatment pathway.

The prescribing of lomitapide and/or LDL apheresis is limited to a few specialist centres in the UK and the number of patients with HoFH in the UK is low, so it is difficult for the EAG to establish how reflective the usage of lomitapide (21.5%) or LDL apheresis (33.8%) in ELIPSE are of UK clinical practice. Nevertheless, the EAG's clinical experts reported that both of these treatments are used in the UK and it is likely that LDL apheresis usage is slightly higher in UK clinical practice compared to in ELIPSE (33.8%).

In summary, the EAG notes the omission of a cost-effectiveness analysis for evinacumab in adolescent patients and considers there to be limited clinical efficacy data for evinacumab in this population; the clinical data are discussed in Section 3.3.4.1. The EAG is also concerned that the background LLT and LDL apheresis usage in ELIPSE may not be representative of the treatments currently used in the UK HoFH population.

2.3.2 Intervention

Evinacumab is a fully humanised recombinant monoclonal antibody for the treatment of HoFH. Evinacumab specifically binds to and inhibits ANGPTL3, which is expressed primarily in the liver. It reduces LDL-C independent of the presence of LDL receptors (LDLR). Evinacumab's mechanism of action leads to lower circulating levels of LDL-C, and thus reduces the risk of atherogenic-mediated cardiovascular disease and mortality.

Evinacumab is an intravenous treatment administered as an infusion over 60 minutes at a dose of 15 mg/kg once every 4 weeks. The company reported that it is intended initially to be prescribed through specialised centres and that it is expected to be administered in outpatient settings.

Evinacumab was granted marketing authorisation by the Medicines and Healthcare products Regulatory Agency (MHRA) in August 2022 for use as an adjunct to diet and other LDL-C lowering therapies in the treatment of adult and adolescent patients aged 12 years and older with HoFH. No dose adjustment is required in adolescent patients or people who are elderly or who have renal or hepatic impairment.

The company reported that evinacumab is a novel, innovative, first-in-class drug and its mechanism of action is independent of pathways targeted by other forms of LLT, including statins and PCSK9 inhibitors.

The EAG notes that the dosing regimen of evinacumab in the ELIPSE trial is consistent with the MHRA marketing authorisation. However, the EAG notes that HoFH is a chronic condition with treatment expected to be lifelong and that there are limited data on the long-term safety and efficacy of evinacumab.

2.3.3 Comparators

The NICE final scope specified the comparators for people aged 18-years and older to be established clinical management without evinacumab including but not limited to statins, diet and lifestyle changes, ezetimibe, lomitapide, evolocumab and LDL apheresis. For people aged 12-17 the comparator was established clinical management excluding lomitapide. The EAG notes that the MHRA marketing authorisation for lomitapide restricts its use to adults and the EAG's clinical experts confirmed that it is not used in patients with HoFH aged under 18 years.

The company considers evinacumab to be a replacement for lomitapide in the treatment pathway, and that lomitapide is the only comparator for the adult population (people aged 18 years or older). No comparators have been considered for the adolescent population in the CS. The EAG's clinical experts reported that lomitapide is not used in all HoFH patients and that the treatments comprising established clinical management are likely to vary between HoFH patients.

At clarification, the EAG requested that the company clarified their choice of comparator and the company reported that *"Evinacumab is intended to replace lomitapide at the same point in the pathway*." Additionally, in the company response to clarification question A1, the company stated: "*LDL apheresis is NOT considered a comparator in any scenario*" and that the position of evinacumab in the treatment pathway for adolescents is the same as for adults, although it is noted that lomitapide is not a treatment option for adolescents. The EAG therefore does not consider the cost-effectiveness results for the comparison of evinacumab versus lomitapide in adults to be relevant for the adolescent population.

The EAG acknowledges that in the new EAS 2023 guidelines evinacumab is positioned alongside lomitapide as a third-line treatment with or without LDL apheresis. Additionally, the EAG notes that patients would continue to receive other background LLTs such as statins, ezetimibe and PCSK9

inhibitors in addition to evinacumab or lomitapide. Established clinical management for HoFH in the UK comprises of the drug classes seen as background LLTs in ELIPSE, and that similar to in ELIPSE, not all patients receive all of the available LLTs. The EAG is therefore concerned with the company's positioning of evinacumab as a replacement for lomitapide as this could be a larger population than those currently receiving lomitapide. That is, the population where clinicians would want to use lomitapide is likely to be larger than the population that receives lomitapide, principally due to toxicity issues. In those patients that clinicians would want to use lomitapide but cannot, the EAG considers that they would receive continued use of LLTs (with or without LDL apheresis). The EAG therefore considers that while lomitapide (with or without LDL apheresis) is a key comparator for the adult population, continuation of background LLTs (without lomitapide) is also a relevant comparator for those patients unsuitable for lomitapide. In addition, the EAG considers that continuation of maximally tolerated background non-lomitapide LLTs is potentially the main comparator for evinacumab in the adolescent population based on the company's proposed positioning for evinacumab.

The EAG also considers that addition of LDL apheresis to continuation of maximally tolerated background LLTs could be considered a comparator for evinacumab based on the new 2023 EAS guidelines. However, the EAG also notes that in the current commissioning policy for lomitapide, LDL apheresis should be given where clinically indicated prior to lomitapide. The EAG therefore considers that based on the company's restricted positioning of evinacumab as a replacement for lomitapide, evinacumab should also be given after LDL apheresis. The MHRA marketing authorisation for evinacumab does not impose any restrictions on its use in the treatment pathway for patients with HoFH and the EAG's clinical experts reported that having evinacumab as a treatment option prior to LDL apheresis would be welcomed in clinical practice. Nevertheless, the company does not consider LDL apheresis to be a relevant comparator for evinacumab.

The EAG notes that there is a lack of head-to-head data for the comparison of evinacumab with lomitapide and that the company has conducted a matching adjusted indirect comparison (MAIC) using the evinacumab arm of ELIPSE and data on lomitapide from Cuchel *et al*.[16] The EAG notes that none of the patients in Cuchel *et al*. were on PCSK9 inhibitors which are now a commonly used background LLT in the UK prior to lomitapide. The efficacy of lomitapide in Cuchel *et al*. may therefore not represent the efficacy in clinical practice today. In addition, the EAG is concerned that not all baseline characteristics have been adjusted for in the company's MAIC (CQ response A15: not matched for sex; body mass index (BMI); method of diagnosis; ethnicity; and background drugs) but

acknowledges that the sample size in both studies is low. The EAG is also concerned that 25.6% of patients in the evinacumab arm of ELIPSE were receiving lomitapide as part of their background LLTs and therefore this may have confounded the results of the MAIC. The EAG requested that the company provided the results of the MAIC excluding the patients in ELIPSE who received lomitapide and the company provided this as a scenario analysis in response to clarification question A16, while highlighting concerns that in this analysis the estimated sample size (ESS) is reduced to 3.9. The EAG agrees this is a low ESS and recommends caution in drawing conclusions using the estimates of efficacy for evinacumab versus lomitapide from the company's MAICs (Section 3.4.4).

In addition, the company presented the results from an unanchored MAIC for evinacumab versus ezetimibe and a Bucher indirect treatment comparison (ITC) for evinacumab versus evolocumab in the CS. The EAG is concerned that these analyses use data from RCTs where patients are randomised to treatment with ezetimibe[18] or evolocumab[19], respectively, rather than continuing on them as background treatment. The EAG therefore does not consider these analyses presented by the company to reflect their proposed positioning of evinacumab in the treatment pathway for patients with HoFH. Furthermore, the EAG disagrees with the company's use (and need) for these results in the economic model as discussed in Section 4.2.7.1 Therefore, the EAG does not discuss the results of these analyses in this report.

The EAG notes from the results of the placebo arm of ELIPSE, that the change in LDL-C from baseline to week 24 was generally small irrespective of the background LLT and clinical experts agreed that little change in LDL-C would be expected in clinical practice once LLT regimens have been stabilised. The EAG therefore considers that the placebo arm of ELIPSE may provide a reasonable estimate of continued background maximally tolerated LLT (with or without LDL apheresis) to enable a comparison with evinacumab for use in a cost-effectiveness analysis. The EAG considers it important to highlight that the ELIPSE data includes some patients on background lomitapide but the EAG considers that including these in the analysis avoids the need to break randomisation and thus results in a more robust analysis. The EAG also considers that subgroup data suggest the inclusion of patients with background lomitapide in the ELIPSE analysis may result in a conservative estimate of the efficacy of evinacumab versus continued background LLT without lomitapide, because placebo patients on background lomitapide have a slightly higher reduction in LDL-C (-17.2 mmol/L) compared to placebo patients not on background lomitapide (4.5 mmol/L).

In summary, the EAG notes that the company considers lomitapide to be the only relevant comparator for evinacumab in adults. The EAG also notes that the only comparative data for the adolescent population presented in the CS is for 2 patients in the ELIPSE trial and that no cost-effectiveness analysis is presented in the CS for the adolescent population.

The EAG is concerned that continuation of background LLT without lomitapide is a potentially relevant comparator for both the adult and adolescent populations, and that this has not been considered in cost-effectiveness analyses presented in the CS. However, the EAG is also concerned that there is a lack of robust clinical data to enable a robust comparison of evinacumab with any of the relevant comparator treatments, and therefore any estimates of clinical efficacy should be interpreted with caution.

In conclusion, the EAG considers the relevant comparators for the company's restricted positioning of evinacumab are:

1) lomitapide with continuation of maximally tolerated background LLTs (including LDL apheresis where appropriate) in the adult population;
2) continuation of maximally tolerated background LLTs (including LDL apheresis where appropriate) in the adolescent population; and
3) continuation of maximally tolerated background LLTs (including LDL apheresis where appropriate) in the adult population unsuitable for lomitapide.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence reporting the clinical efficacy and safety of evinacumab and relevant comparator therapies for the treatment of HoFH. The company reported that the searches were designed to meet the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[20] Methods and search results for the company's SLR are provided in Sections B.2.1, B.2.2 and Appendix D of the company submission (CS) and the EAG critique of the methods is provided in Table 12 below.

The clinical SLR searches were initially conducted on 28 March 2022 and updated on 13 March 2023. Additional searches to identify observational and real-world evidence were conducted in February 2023. The company's SLR identified 29 studies from 40 publications, and four of the studies related to evinacumab. The EAG notes that only three of the evinacumab studies were discussed in detail in the CS, with the remaining study (Reeskamp *et al.* 2021) excluded due to a small sample size (n=4) and its primary purpose being to investigate pharmacokinetics rather than clinical efficacy. The EAG considers this exclusion to be reasonable; the EAG critique of the remaining three evinacumab studies is provided in Section 3.3.

The EAG notes that the remaining 25 included studies relate to comparators and the only study considered in detail by the EAG is the study used in the company's MAIC for the comparison of evinacumab versus lomitapide: Cuchel *et al.* 2013.[16] As discussed in Section 2.3.3, the EAG does not consider the included studies on evolocumab or ezetimibe to reflect the companies proposed positioning of evinacumab in the treatment pathway.

In summary, the EAG considers the company SLR searches to be appropriate and unlikely to have missed any relevant studies for evinacumab or lomitapide.

Table 12. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	D.1.4.1.2	**The EAG considers the sources and dates searched to be appropriate and comprehensive.** Databases searched were as follows:

		• Embase (OvidSP); • MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE<1946 to Present>, MEDLINE In-Process Citations & Daily Update (OvidSP); • ClinicalTrials.gov; • WHO ICTRP; and • Cochrane Central Trials Register (CENTRAL). Database searches for: Phase 2/3 studies, RCTs, Non-RCTs (both controlled and single arm trials), and Phase 4 studies, were performed from inception on the 28 March 2022, with update searches conducted on 13 March 2023. In addition, database searches for RWE (defined as prospective and retrospective observational studies) were conducted on 28 February 2023. Hand searching of bibliographies of identified systematic reviews was also conducted.
Search strategies	D.1.4	**The EAG considers the search strategies used likely to be appropriate but notes that search filters were used to limit by study design for the searches in MEDLINE and Embase** Search terms comprised a combination of terms for familial hypercholesterolaemia and the interventions of interest. Search terms for study designs of interest were also included, and limits restricting to English language publications were applied. The search terms included a mixture of MeSH indexing and free-text terms.
Inclusion criteria	D.1.3	**The EAG considers the inclusion criteria for the SLR to be reasonable.** For inclusion, studies were required to comprise of adults and/or adolescents (age ≥ 12 years) with HoFH. Studies that reported on mixed populations were excluded unless they reported relevant subgroup analyses and studies with a sample size of n≤2 were also excluded. The following interventions either alone or in combination with other pharmacological interventions were deemed suitable for inclusion: • Evinacumab; • Lomitapide; • Ezetimibe; • PCSK9 inhibitor: evolocumab; and • LDL apheresis.
Screening	D.1.3	**The EAG considers the methods for screening to be robust.** Records were screened by two independent analysts at both title and abstract review and full text review. Where there was disagreement that could not be resolved by consensus, a third analyst was involved to make a final decision. Results of the literature screening processes were summarised in a PRISMA diagram.
Data extraction	D.1.1	**The EAG considers the methods for data extraction to be unclear.** There were no explicit details reported in the CS or CS appendices on the methods used for data extraction in the clinical SLR although the company cites varies UK and international guidance for the methods used in the company's clinical SLR.
Tool for quality assessment	D.4	**The EAG considers the company's choice of quality assessment tools to be reasonable.**

of included study or studies		The ELIPSE RCT was assessed using both the RoB2 tool and the tool recommended in the NICE methods manual.[21, 22] Additional included RCTs were assessed using only the NICE methods ROB tool. The Cuchel *et al.* study on the comparator, lomitapide, was assessed using the ROBINS-I tool and the Newcastle-Ottawa scale.[23] [24] The remaining single-armed or observational studies were assessed using the Newcastle-Ottawa scale.[24]

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; CS, company submission; EAG, External Assessment Group; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; RCTs, randomised controlled trials; ROB, risk of bias; SLR, systematic literature review; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

3.2 Critique of trials of the technology of interest

In total, three studies of evinacumab were included in the CS:

- ELIPSE (R1500-CL-1629, NCT03399786)[13] – a 24-week Phase 3 parallel group, placebo-controlled RCT of evinacumab versus placebo in people aged ≥12 years with HoFH (n=65) and with single-armed data from an open label extension up to 48 weeks (n=[redacted]; data on file [25]);
- Study R1500-CL-1331 (NCT02265952)[26] – a 16-week Phase 2, open-label, single-armed, proof-of-concept study in adults aged ≥18 years with HoFH (n=9); and
- Study R1500-CL-1719 (NCT03409744)[10] – results presented from an interim analysis of the ongoing open-label long-term study on the safety and efficacy of evinacumab with a planned follow up of up to 192 weeks in people aged ≥12 years with HoFH (n=[redacted]) and it included evinacumab naïve patients (n=[redacted]) in addition to enrolling patients from ELIPSE (n=[redacted]) and Study R1500-CL-1331 (n=[redacted]).

The EAG notes that the dosing regimen of evinacumab used in Study R1500-CL-1331 was not consistent with the recommended dose for use in England in the MHRA marketing authorisation (evinacumab 15 mg/kg intravenously once every four weeks [IV Q4W]). Additionally, the dose and route of administration varied during Study R1500-CL-1331:

- Starting dose: evinacumab 250 mg subcutaneously (SC);
- Week 2 to 12: evinacumab 15 mg/kg IV once weekly (QW); and
- Week 13 to 16 (end of treatment): evinacumab 450 mg SC.

The dose of evinacumab in both ELIPSE and Study R1500-CL-1719 (long-term) were consistent with the marketing authorisation for England (15 mg/kg IV Q4W). The EAG therefore does not consider the results from Study R1500-CL-1331 of relevance to the decision problem and does not discuss this study or its results further although it is detailed in the CS.

The EAG is also concerned that in Study R1500-CL-1719 (long-term) the baseline for the [redacted] patients enrolled from Study R1500-CL-1331 was defined as the last obtained value before the first dose of study drug in Study R1500-CL-1719;

[redacted]

The results from the long-term study are presented for the full trial population, and by the subgroups of evinacumab naïve patients, and the patients deemed to continue evinacumab (i.e. enrolled from the previous two trials). The EAG notes that for the subgroup of patients who continued from ELIPSE,

[redacted]

The results reported for Study R1500-CL-1719 were from an interim analysis where only [redacted]% of patients had completed the study but it was reported in the CS that the study was completed in April 2023. The EAG is unclear when the final analysis of Study R1500-CL-1719 will be available but considers it will provide more robust data on the long-term efficacy and safety of evinacumab.

The EAG notes that the efficacy data in Study R1500-CL-1719 beyond week

[redacted]

[redacted]

In summary, the EAG considers the 24-week double-blind study period from ELIPSE to provide the most robust comparative data for evinacumab versus continuation of background LLT. The EAG also considers the data from the single-arm extension period of ELIPSE, and the single-arm Study R1500-CL-1719, to provide important data of relevance on the long-term safety and efficacy of evinacumab albeit non-comparative data. The EAG notes that the company only uses data from the double-blind treatment period of ELIPSE in its analyses of cost-effectiveness and the EAG therefore focuses its critique on these data. However, the EAG notes that the Study R1500-CL-1719 includes [redacted] adolescent patients and given that only one patient in ELIPSE received evinacumab during the double-blind treatment period, the EAG considers the efficacy data from Study R1500-CL-1719 are of importance to the decision problem. The EAG therefore also provides an overview of Study R1500-CL-1719 with comparison between the total population and the adolescent subgroups in the subsections below.

3.2.1 Overview and critique of the ELIPSE study

The EAG's assessment of the design, conduct and internal validity of the ELIPSE[13] trial is summarised in Table 13. The EAG broadly agrees with the company's assessment of ELIPSE as generally being at low risk of bias for analysis of the primary outcome assessment at week 24, although as discussed in Section 2.3.1, the EAG is concerned about the low proportion of adolescents enrolled in the trial. The EAG is also concerned that the background LLT and LDL apheresis usage in ELIPSE may not be representative of the treatments currently used in England for HoFH and that there were patients on lomitapide at baseline in both arms of ELIPSE (Section 2.3.1).

Table 13. EAG's summary of the design, conduct and analysis of ELIPSE[13]

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	B.2.3.1.4 and	**Appropriate** Patients were randomised in a 2:1 ratio to evinacumab 15 mg/kg IV Q4W (n=43) or placebo (n=22) using an interactive voice- or Web response system. Randomisation was stratified by apheresis treatment (yes or no) and geographical region (Japan and rest of the World).

Concealment of treatment allocation	Appendix D.4	**Likely to be appropriate** Details of the method of allocation concealment in the CS are limited but the EAG notes an interactive voice- or Web-response system was used in the allocation of patients to study treatment. Unfortunately the EAG did not have access to the trial protocol for ELIPSE for further detail.
Eligibility criteria	B.2.3.1.3 and Table 7	**Likely to be appropriate** The EAG notes that 32% of patients in ELIPSE had a clinical diagnosis of HoFH rather than a genetic diagnosis and the EAG's clinical experts reported that patients in the UK would generally be expected to have a genetic diagnosis. However, the EAGs clinical experts also reported that the clinical diagnostic criteria in ELIPSE appear reasonable. Study treatment in ELIPSE was added on to the patients' stable background LLT and patients were required to be on a maximally tolerated statin, ezetimibe, and a PCSK9 inhibitor antibody (unless the patient had a documented reason not to be). Patients receiving LDL apheresis were also included (only weekly or bi-weekly schedules were allowed). The background LLTs and LDL apheresis schedules of patients were required to be stable by the screening visit but there was an 8-week run in prior allowed prior to screening. The EAG's clinical experts reported that the inclusion and exclusion criteria of ELIPSE appeared reasonable although there were some concerns with the resulting population, mainly in relation to the background LLTs which are discussed under the baseline characteristics below.
Blinding	B.2.3.1.4	**Appropriate** ELIPSE was a double-blind RCT with patients and the treating physicians blinded to study treatment, and both study drugs: evinacumab and placebo, were supplied in physically identical vials with the same withdrawal volume. Additionally the EAG notes that the primary outcome was an objective measure: change from baseline in LDL-C and so blinding is less important compared to for subjective outcome measures such as HRQL.
Baseline characteristics	B.3.2.1.8	**Not representative of the whole population eligible for evinacumab in UK clinical practice** Only 2 adolescent patients (aged 12 to 17 years) were enrolled in ELIPSE and additionally the background LLTs used at baseline in ELIPSE may not be reflective of current UK clinical practice or in line with the company's positioning of evinacumab in the treatment pathway. The EAG's clinical experts reported that statin (93.8% in ELIPSE), ezetimibe (75.4%) and LDL apheresis (33.8%) usage maybe higher in the UK. In addition, the EAG notes 25.1% of patients were on lomitapide as a background LLT a baseline in ELIPSE.
Dropouts	B.2.3.1.7	**Appropriate** A total of 64 patients (98.5%) completed the DBTP. One patient in the placebo group withdrew consent and discontinued study treatment early.
Statistical analysis		
Sample size and power	B.2.4.1.1	**Appropriate** The company reported that: "It was estimated that a sample size of 57 patients (38 assigned to receive evinacumab and 19 assigned to receive placebo) was required to provide a power of 90% to confirm the primary efficacy hypothesis of a between-group absolute difference in the mean

		percent change in the LDL-C level of 38 percentage points, according to a two-sample t-test with a two-sided significance level of 0.05.". The EAG notes that the sample size was met and the study was powered appropriately for assessment of the primary efficacy outcome based on the study protocol and absence patients withdrawing from the study during the double-blind treatment period.
Handling of missing data	B.2.4.1.2 and B.2.4.1.3	**Appropriate** A mixed-effects model for repeated measures was used to analyse the percent change from baseline in the calculated LDL cholesterol level at Week 24 in the ITT population. In the CSR it is reported that: "[redacted]
Outcome assessment	B.2.4.1.2 to B.2.4.1.5	**Appropriate** Three datasets were analysed; these were the efficacy analysis set, safety analysis set (SAF), and a quality of life (QoL) set. The EAG notes that the efficacy Sets included the ITT population (defined as all randomised patients who received at least 1 dose or part of a dose of evinacumab in the DBTP), and the mITT population (defined as the randomised population who took at least 1 dose or part of a dose of evinacumab in the DBTP and had an evaluable primary endpoint). Both the ITT and mITT included all 65 randomized patients (100.0%). The SAF also included all 65 patients [redacted] The QoL analysis set included only 63 patients, [redacted]

Abbreviations: DBTP, double-blind treatment period; EAG, External Assessment Group; ITT, intention-to-treat; LDL-C, low-density lipoprotein-cholesterol; LLT, lipid lowering therapy; mITT, modified intention-to-treat; Q4W, every 4 weeks; QoL, quality of life; SAF, safety analysis set.

3.2.2 Overview and critique of Study R1500-CL-1719 (long-term safety and efficacy interim analysis)

As noted above, Study R1500-CL-1719 is a single-arm, open-label, long-term study on the safety and efficacy of evinacumab with a planned follow up of up to 192 weeks.[10, 27] The results presented in the CS were from an interim analysis ([redacted]% of patients were ongoing in the treatment period of the study), despite the study being completed in April 2023. The EAG notes that results from the final analysis have not been published yet, and the company did not provide results from the final analysis in the CS.

Patient enrolment in Study R1500-CL-1719 comprised of patients who had completed two previous studies: the ELIPSE trial (R1500-CL-1629 [ELIPSE]) ([redacted]), and the proof-of-concept trial (R1500-CL-1331) ([redacted]), as well as evinacumab naïve patients ([redacted]). Inclusion criteria for Study R1500-CL-1719 required HoFH patients to be aged ≥12 years and receiving maximally tolerated LLTs (statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, lomitapide, and/or lipoprotein apheresis). The study included a 10-week run-in period for patients who needed stabilisation on background LLT and/or LDL apheresis and a 2-week screening period for patients on stable background LLT unless they had completed an end of study visit for their previous evinacumab study within 7 days. All patients in Study R1500-CL-1719 received evinacumab 15 mg/kg IV administered Q4W from day 1 and following the end of treatment were to be followed up for 24 weeks after receiving the last dose of study drug.

The EAG considers the baseline characteristics of patients enrolled in Study R1500-CL-1719 [redacted]. In Study R1500-CL-1719, background LLTs included [redacted]

The company reported that the no formal analysis of study quality was conducted. The EAG notes the observational, single-arm, open-label design of the study and that the results of Study R1500-CL-1719 were not used in the economic analyses. Results of the study are presented in the subsections below with particular focus on the adolescent subgroup and the comparability of the results with the overall trial population (Section 3.3.4.1.2).

3.3 Critique of the clinical effectiveness analysis and interpretation

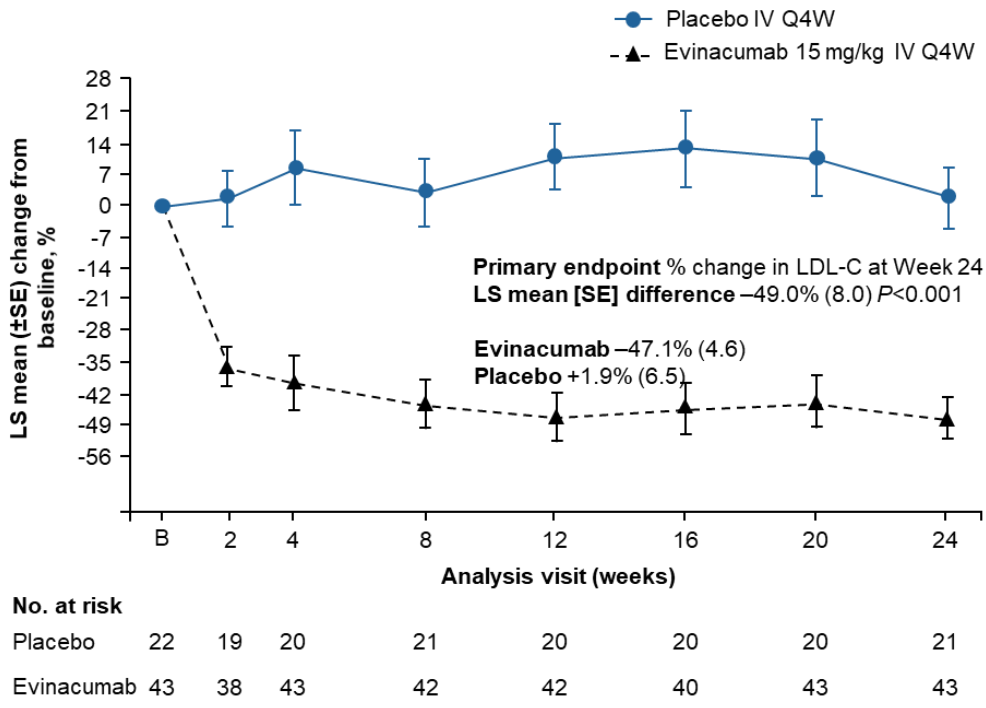
Results presented here focus on changes in LDL-C, as this was the only clinical outcome from the clinical trials that was used in the company's base case for the analysis of cost-effectiveness. A brief overview of other efficacy outcomes from ELIPSE and Study R1500-CL-1719 that are of relevance to the NICE final scope is also provided below.

3.3.1 *Primary outcome: Changes in LDL-C levels*

3.3.1.1 *ELIPSE trial results*

The primary efficacy outcome of the ELIPSE trial was the percent change in calculated LDL-C from baseline to week 24[13] and evinacumab demonstrated a statistically significant reduction in LDL-C versus placebo with a least squares (LS) mean difference of -49.0% (95% CI: -65% to -33.1%; p<0.001 for evinacumab versus placebo [Figure 2]). The LS mean percentage change from baseline in calculated LDL-C at week 24 was -47.1% in the evinacumab treatment arm compared with +1.9% in the placebo arm of ELIPSE. The LS mean absolute change from baseline in calculated LDL-C at week 24 was -134.7 mg/dL (-3.48 mmol/L) for the evinacumab treatment arm compared with +2.6 mg/dL (+0.07 mmol/L) for the placebo arm. The LS mean difference in absolute change from baseline in calculated LDL-C at week 24 for evinacumab versus placebo was also statistically significant (-132.1 mg/dL; p<0.001 [CS Figure 14B]).

Figure 2. Percentage change in LDL-C from baseline to week 24 in ELIPSE (Reproduced from CS, Figure 14A)



Abbreviations: IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LS, least squares; Q4W, every 4 weeks; SE, standard error.

During the open-label treatment period of ELIPSE, the results demonstrated [redacted] percentage change in LDL-C from baseline to week 48 for evinacumab patients who continued on evinacumab (n=[redacted]) compared with the results for change from baseline

to week 24, with a percentage change in LDL-C from baseline to week 48 of [redacted] (baseline to week 24: -47.1%). As placebo patients switched to evinacumab during the open-label treatment period (n=[redacted]), there is no comparative data for placebo. The EAG notes the percentage change in LDL-C from baseline to Week 48 was [redacted] for placebo patients who commenced evinacumab at week 24; this is a [redacted] compared to that seen at week 24 in the evinacumab group treated during the double-blind treatment period ([redacted]

[redacted]_(Reproduced from CS, Figure 15).

[redacted]

3.3.1.2 Study R1500-CL-1719 results (long-term safety and efficacy interim analysis)

Results from the interim analysis of Study R1500-CL-171 for change in LDL-C from baseline are provided in[redacted]but the EAG recommends caution in interpreting these data as

[redacted]

[redacted]

(Reproduced from CS, Figure 16)

[redacted]

[redacted].

[redacted] provides the relative and absolute reduction in LDL-C associated with evinacumab up until [redacted] weeks for the overall combined study population in Study R1500-CL-1719. In the total population, treatment with evinacumab resulted in a [redacted]

[redacted]

*(Reproduced from CS, Figure 17)

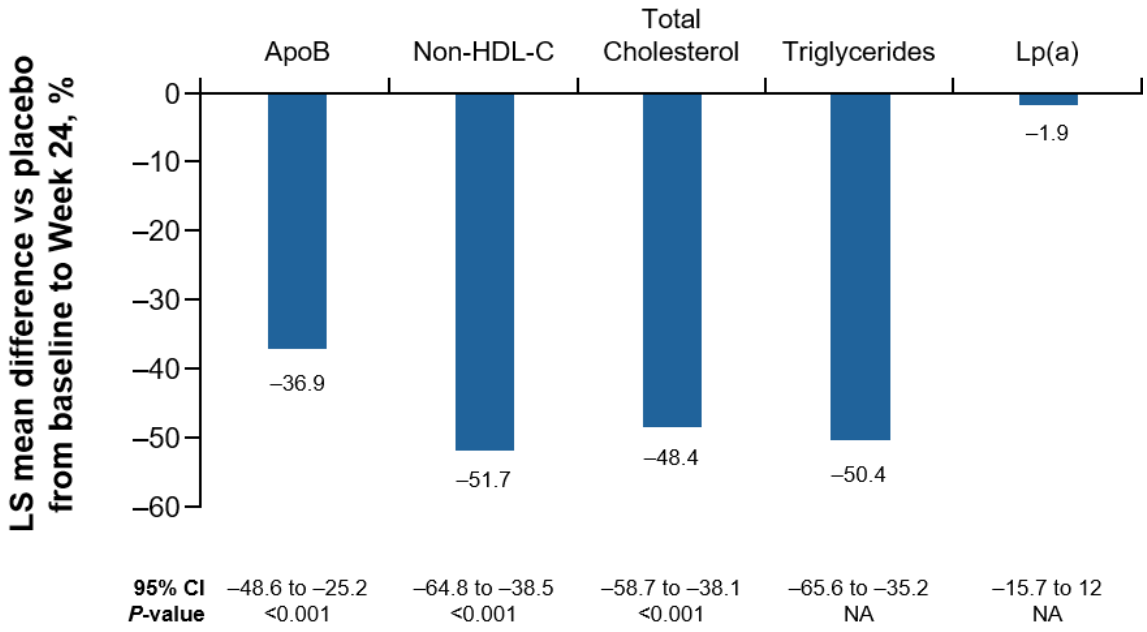
3.3.2 Secondary outcomes

3.3.2.1 ELIPSE trial results

Treatment with evinacumab in ELIPSE resulted in statistically significant percentage reductions from baseline in apolipoprotein B, non-HDL-C, and total cholesterol from baseline to week 24 compared with placebo (all p<0.001; Figure 6).

The company also reported that evinacumab resulted in an approximately -30% change in HDL-C at week 24 but the EAG is unclear of the clinical significance of this; the EAG notes from HEART UK that HDL cholesterol can have a protective role against heart attacks and strokes, and therefore a reduction in HDL-C may not be clinically beneficial.[28]

Figure 6. LS mean difference versus placebo from baseline to Week 24 in ELIPSE (Reproduced from CS, Figure 18)



Abbreviations: ApoB, apolipoprotein B; CI, confidence interval; Lp(a), lipoprotein(a); LS, least squares; non-HDL-C, non-high-density lipoprotein cholesterol.

In the CS, the company reported the percentage of patients who met US lipoprotein apheresis eligibility criteria (LDL-C ≥300 mg/dL) was numerically lower in the evinacumab group (7%) compared with the placebo group (23%) at week 24 but the EAG notes that the difference in odds ratio did not reach statistical significance (p=0.09). The EAG also notes that in the CSR for ELIPSE, results are also available for the percentage of patients who met the EU apheresis eligibility criteria as outlined by the German Apheresis Working Group:[29] treatment required for primary CVD prevention and LDL-C >160 mg/dL (4.2 mmol/L) or treatment required for secondary CVD prevention and LDL-C >120 mg/dL (3.1 mmol/L). The results from ELIPSE at week 24 using the EU apheresis eligibility criteria

[redacted]

3.3.2.2 Study R1500-CL-1719 results (long-term safety and efficacy interim analysis)

The results from the interim analysis of Study R1500-CL-1719 at [redacted]

[redacted]

3.3.3 Quality of life

EQ-5D data were collected during ELIPSE, although the EAG notes they were not used in the company's economic model base case. The EAG notes that there were reductions in mean utility score in both the placebo and evinacumab arms from baseline to week 24, although the company reported that they were not statistically significant. The company reported that the EQ-5D results, "*can be likely explained by the insensitivity of the EQ-5D measure in this patient population, due to the episodic nature of the condition, i.e., QoL being more dependent on CV events rather than direct LDL-C change*". The EAG notes that the mean changes in EQ-5D utility score are numerically small in both trial arms: -0.0189 in the evinacumab arm and -0.0593 in the placebo arm at week 24.

3.3.4 Subgroup analyses

3.3.4.1 Adolescent patients

3.3.4.1.1 ELIPSE trial results

There were only two patients aged between 12 and 18 years enrolled in ELIPSE and so meaningful conclusions cannot be drawn from the subgroup analysis. The percent change from baseline in LDL-C at Week 24 for the adolescent patient treated with evinacumab was -73.3% and for the adolescent patient treated with placebo it was +60%. The company reported that both adolescent patients were null/null (data on file).

The EAG notes that the LS mean percentage change from baseline in calculated LDL-C at week 24 was -47.1% in the evinacumab treatment arm of ELIPSE for the full trial population and the result for the adolescent patient therefore appears to be consistent with the overall trial.

3.3.4.1.2 Study R1500-CL-1719 results (long-term safety and efficacy interim analysis)

The long-term safety and efficacy study (R1500-CL-1719) enrolled [redacted]

[redacted] (Reproduced from CS, Figure 21)

[redacted]

[redacted]

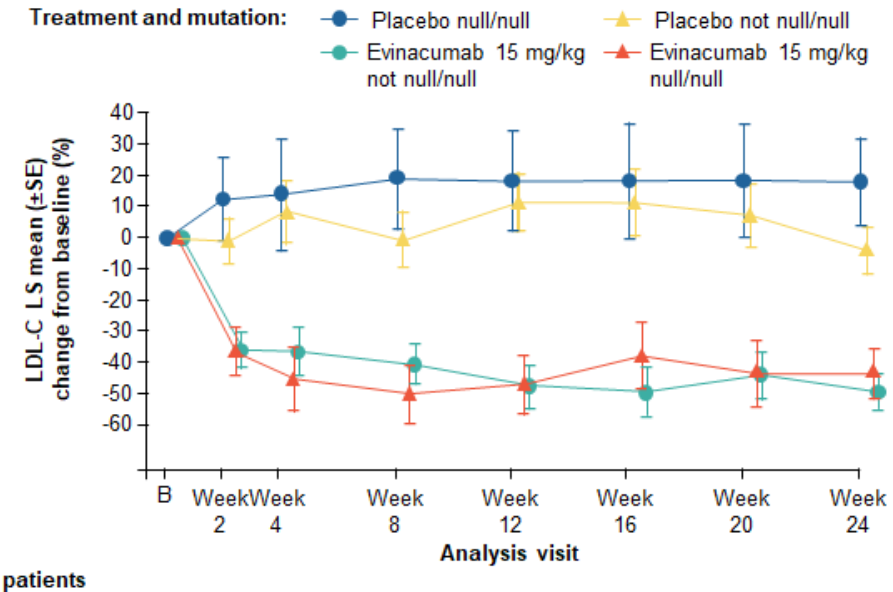
3.3.4.2 Mutation status

ELIPSE included all patients with HoFH regardless of their LDLR genetic mutations. A total of 21 patients (32.3%) had mutations defined as null/null with minimal LDLR activity (defined as <15% based on *in vitro* assessments of functionality as reported in the literature).[30] In addition, the company reported in response to clarification that [redacted] were classified as negative/negative ([redacted] in the placebo arm and [redacted] in the evinacumab arm), defined as stop codons, frame shifts, splice site changes, small and large insertions/deletions and copy number variations resulting in the LOF of both LDLR alleles.

The mean baseline LDL-C for patients with null/null mutations was 311.5 mg/dL (8.06 mmol/L), and for patients with negative/negative mutations it was 289.4 mg/dL (7.48 mmol/L). The company reported that this was considerably higher than the mean LDL-C for those patients not considered to have these mutations (246.5 mg/dL [6.39 mmol/L] for the whole cohort). The EAG notes that this finding is consistent with published literature and that these subgroups of patients with null/null and negative/negative mutations are typically less responsive to some of the existing LLTs.[31]

Treatment with evinacumab resulted in an approximately -50% mean change in LDL-C from baseline to Week 24 for patients with HoFH, regardless of their genotype (Figure 8). In terms of absolute mean change in LDL-C, the change for patients with null/null mutations was -158.8 mg/dL (-4.11 mmol/L), and -142.0 mg/dL (-3.67 mmol/L) for patients with negative/negative mutations.[13, 32] [redacted]).

Figure 8. Calculated LS mean (±SE) percent change in LDL-C from baseline to Week 24 by null/null mutation status in both LDLR alleles (Reproduced from CS, Figure19)



No patients								
P null/null n=6	5	4	5	5	5	5	5	5
P not null/null n=16	16	15	14	15	14	14	14	15
E 15 mg/kg null/null n=15	15	14	15	15	14	15	15	15
E 15 mg/kg not null/null n=28	28	24	28	27	28	25	28	28

Notes: Data are for the <15% LDLR activity population. LS means and SEs are taken from a mixed-effect model with repeated measures approach with the fixed categorical effects of treatment group, randomization strata (lipoprotein apheresis [yes/no] and region [Japan, rest of world]), subgroup factor, time point, treatment-by-time point interaction, strata-by-time point interaction, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as continuous fixed covariates of baseline calculated LDL-C value and baseline value-by-time point interaction. Data adapted from Raal et al. 2020.[13]

Abbreviations: B, baseline; E, evinacumab; LDL, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LS, least squares; P, placebo; SE, standard error.

3.3.4.3 Background LLT

Continuation of background LLT is a comparator of interest in the NICE final scope and therefore the EAG considers the subgroup results from ELIPSE by background LLT to be of relevance. The EAG notes that regardless of background LDL-C-lowering therapies (statins, ezetimibe, PCSK9 inhibitor, lomitapide, LDL apheresis), evinacumab resulted in approximately a -50% mean change in LDL-C from baseline to week 24 (Table 14; Figure 9).

The company reported in response to clarification question A22, that the results provided in Table 14 were not calculated using the same methods used for the primary outcome assessment in ELIPSE (mixed-effects model for repeated measures); the company reported that the results provided in

Table 14 are descriptive summaries. The EAG is unclear what impact using mixed-effects model for repeated measures would have on these subgroup results.

The EAG notes from the company response to clarification question A5, that [redacted]. Results for this subgroup are not provided but the EAG considers it important to highlight that [redacted] in ELIPSE and thus not consistent with the company's positioning of evinacumab in the treatment pathway. In addition, the EAG notes from the company response to clarification question A6 that approximately [redacted] ELIPSE who were on lomitapide at baseline had null/null mutations.

Table 14. Percent change in LDL-C from baseline to Week 24 by background LLT (Reproduced from CS, Table 17)

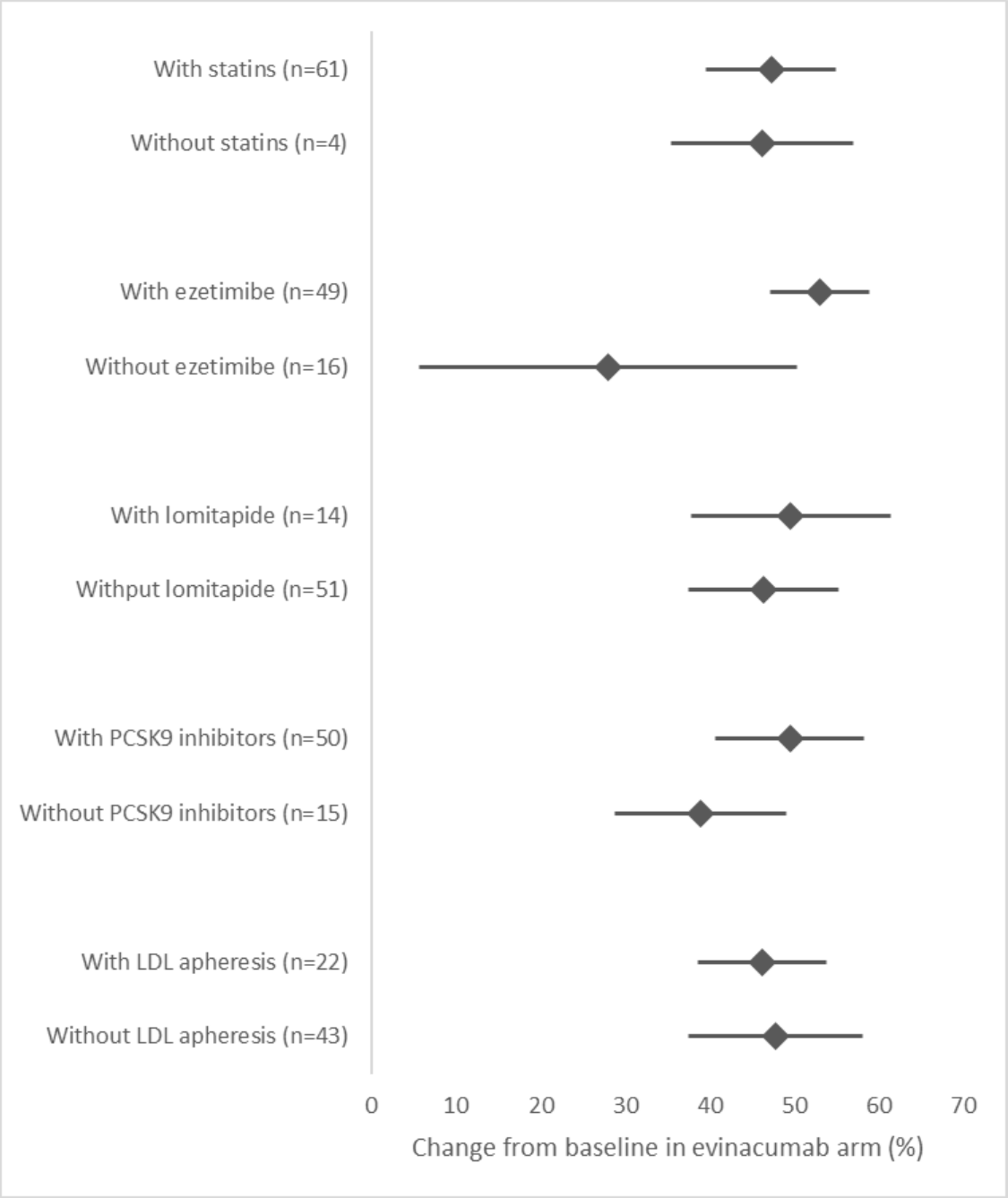
Background therapy at baseline, mean (SD)*	Background therapy at baseline		No background therapy at baseline	
	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W
Statin	n=61		n=4	
	2.2 (32.3)	-47.3 (30.6)	-5.7 (22.7)	-46.2 (11.0)
Ezetimibe	n=49		n=16	
	-2.0 (30.6)	-53.1 (21.0)	12.2 (34.1)	-28.0 (45.5)
Lomitapide	n=14		n=51	
	-17.2 (47.6)	-49.6 (22.5)	4.5 (28.4)	-46.4 (32.3)
PCSK9 inhibitor	n=50		n=15	
	1.7 (30.3)	-49.5 (31.9)	0.7 (36.2)	-38.9 (20.1)
Lipoprotein apheresis	n=22		n=43	
	-7.3 (34.3)	-46.2 (18.1)	6.8 (29.2)	-47.8 (34.4)

Abbreviations: IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, once every 4 weeks; SD, standard deviation.

* Patients taking these medications with or without other medications.

Data from Raal et al. 2020.[13]

Figure 9. Forest plot for percent change in LDL-C from baseline to Week 24 by background LLT in ELIPSE (Reproduced from company response to CQ A10)



3.3.5 Safety

The EAG notes that no adverse event data from the evinacumab trials were used in the company's economic model, although comprehensive AE data from each of the three main evinacumab studies was provided in the CS. The EAG focuses its critique of the safety data below on the double-blind treatment period from ELIPSE.

At least one treatment-emergent adverse event (TEAE) was experienced by a total of 29 patients (65.9%) in the evinacumab treatment group and 17 patients (81.0%) in the placebo treatment group (Table 15). No patients experienced a TEAE leading to death or discontinuation of study treatment but two patients (4.5%), both in the evinacumab treatment group, experienced a serious TEAE (SAE). The two SAEs were urosepsis and suicide attempt, with neither considered to be related to the study drug. Additionally, it was reported that there were no suspected major adverse cardiovascular events during the double blind treatment period of ELIPSE.

Table 15. Overview of Adverse Event Profile: TEAEs During the DBTP of ELIPSE (Safety Analysis Set) (Reproduced from CS, Table 22)

Adverse event	Placebo IV Q4W (n=21)	Evinacumab 15 mg/kg IV Q4W (n=44)
Patients with any TEAE	17 (81.0%)	29 (65.9%)
Patients with at least one serious TEAE	0	2 (4.5%)
Patients with at least one TEAE resulting in discontinuation of treatment	0	0
Patients with any TEAE resulting in death	0	0

Abbreviations: DBTP, double-blind treatment period; IV, intravenous; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event.
Data from Raal et al. 2020.[13]

In terms of TEAEs classified by the investigator as related to study treatment, events were reported for a total of 5 patients (11.4%) in the evinacumab treatment group and 1 patient (4.8%) in the placebo group. The treatment-related TEAEs in the evinacumab arm were infusion site pruritus and nasopharyngitis (2 patients each), and pyrexia, gastroenteritis, muscular weakness, epistaxis, upper respiratory tract inflammation, and vascular pain (1 patient each). The treatment-related TEAEs experience by the one patient in the placebo group were face oedema and infusion site hypoaesthesia.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

As discussed in Section 2.3.3, the EAG considers only the company's MAICs with lomitapide of relevance to the decision problem and therefore the indirect comparisons reported by the company for the comparison with ezetimibe and evolocumab are not discussed below.

In addition, to the MAICs with lomitapide, the EAG provides a critique of the data available for LDL apheresis in Section 3.5.

3.4.1 *Trials informing the indirect treatment comparison with lomitapide.*

The ELIPSE trial was used as the source of clinical effectiveness data for evinacumab and studies on lomitapide were identified from the company's clinical SLR (CS, SectionB.2.1 and Appendix D). The company reported that one study (Cuchel *et al.* 2013),[16] reporting on treatment of people with HoFH using lomitapide was deemed suitable for use in an MAIC.

Cuchel *et al.* 2013 was a single-armed, multicentre, open-label trial with a follow-up period of 56 weeks and there was also an associated open-label extension study with patients followed up to a maximum of 294 weeks (Blom *et al.* 2016).[33] A total of 29 patients entered the main efficacy treatment evaluation period in the Cuchel *et al.*, although 6 patients discontinued (21%) and four of these discontinuations were due to AEs. Missing data were imputed using the last observation carried forward (LOCF) method.

The company conducted critical appraisals of Cuchel *et al.* using the Newcastle Ottawa scale,[24] where it was judged to be at high risk of bias (CS Appendix D.4, Table 15) and using the ROBINS-I tool,[23] where it was considered to be at serious risk of bias (Appendix D.4, Table 14). Particular concerns of note included that the per protocol results were published in the primary publication by Cuchel *et al.,* although the protocol specified the primary outcome was to be reported using an ITT analysis (NCT00730236),[34] and that the authors did not report the method they used to select patients for study inclusion.

ELIPSE was judged to be at low risk of bias, and in the double-blind phase of the ELIPSE trial there were no discontinuations in either arm of the study following randomisation, thus the ITT, modified ITT (mITT), and PP groups were equivalent (evinacumab arm n=43).[13]

The EAG notes that baseline statin and ezetimibe use in ELIPSE and Cuchel *et al.* were reasonably similar but is concerned that 25.6% of patients in the evinacumab arm of ELIPSE received background therapy with lomitapide (n=11), which could potentially confound the results of the MAIC. The EAG notes that the company's proposed positioning of evinacumab in the treatment pathway is at the same point as lomitapide and not as an additional treatment for patients already on lomitapide. The EAG therefore considers that the patients in the evinacumab arm of ELIPSE should not be on lomitapide to ensure results of the MAIC align with the company's proposed positioning of evinacumab. During clarification, the EAG therefore requested the company to

provide the results of an MAIC for evinacumab excluding lomitapide (using the ELIPSE data) versus lomitapide; the results of this analysis are discussed in Section 3.4.4.

In addition, the EAG notes that LDL apheresis usage was much higher in Cuchel *et al.* compared to in the evinacumab arm of ELIPSE (62.1% versus 32.6%, respectively) but acknowledges the subgroup analyses from ELIPSE suggest background LDL apheresis usage didn't impact the percentage mean change in LDL-C seen with evinacumab. However, a greater concern is that Cuchel *et al.* did not include patients on PCSK9 inhibitors because the study was conducted prior to the introduction of PCSK9 inhibitors into routine clinical practice for HoFH. The EAG is therefore concerned about the comparability and relevance of the findings in Cuchel *et al.* to clinical practice today given the lack of patients on PCSK9 inhibitors in the study, and considers it to be unknown what impact this has on the results of the MAICs. However, the EAG notes that in the discussion section of the study publication for Cuchel *et al.* it is reported that the percentage reduction in LDL-C was "*similar to that observed during lomitapide monotherapy in HoFH patients*" from another publication,[35] and this therefore suggests lomitapide has similar efficacy when added to existing background LLTs.

3.4.2 Statistical methods for the matching adjusted indirect comparison (MAIC) with lomitapide

A matching adjusted indirect comparison (MAIC) was undertaken to compare the evinacumab patients from the double blind treatment period of ELIPSE with the lomitapide patients from the ITT population of the Cuchel *et al.* study. Patients treated with evinacumab in ELIPSE were assigned statistical weights to adjust for their over- or under-representation relative to the average prognostic factors and treatment effect modifiers observed in Cuchel *et al.*. These weights were then incorporated into the analyses.

The company reported that they identified prognostic factors using clinical expert advice and from assessment of the evidence base. The resulting prognostic factors included in the MAIC were: age, history of CHD and baseline LDL-C level. In addition, LDL-R mutation status defective/defective or null/null were considered to be potential prognostic factors but were not reported by Cuchel *et al.*, and so could not be incorporated into the MAIC. In response to clarification question A15, the company reported that it would also potentially be possible to further match based on sex, body mass index (BMI), method of diagnosis, ethnicity, and background LLT. The EAG considers it best practice to adjust for all baseline characteristics reported in the relevant studies given the difficulty

in confirming which factors are prognostic/effect modifying. However, the company considered it not to be feasible to match with any more factors due to the limited sample size of both studies.

The company conducted sensitivity analyses with matching performed using the age criteria only, and with the patients receiving concomitant lomitapide removed from the evinacumab arm of the ELIPSE population. The EAG considers the fully adjusted MAIC excluding lomitapide patients from the evinacumab arm to be the most relevant to the decision problem.

The EAG notes that the only outcome considered in the MAICs was percentage change from baseline in LDL-C. Data from 24 weeks were used for evinacumab and data from 26 weeks were used for lomitapide. The EAG considers this reasonable given the availability of data from the two studies. In addition, the EAG notes that both studies had long-term extension studies but the company considered attrition to be a serious issue for Cuchel *et al.* (the lomitapide study), as patient attrition exceeded 20%, and therefore did not consider it appropriate to use these data. Due to time constraints the EAG was unable to assess the feasibility of conducting analyses using data from a later timepoint but considers it would be useful to see how the longer term efficacy of the two drugs compare.

3.4.3 Baseline characteristics for the MAICs versus lomitapide

The baseline characteristics for the evinacumab arm of ELIPSE before and after matching are presented alongside those for Cuchel *et al.* in Table 16 for the analysis including evinacumab patients from ELIPSE with lomitapide at baseline. The EAG considers the main analysis to be the most robust source of efficacy data for evinacumab versus lomitapide and considers it important to highlight that the outcome of interest in the MAIC is change in LDL-C from baseline.

The baseline characteristics for the MAIC excluding patients on lomitapide at baseline in the evinacumab arm of ELIPSE were not provided by the company. However, the EAG notes that in the main analysis, when all the matching variables were applied, the estimated sample size (ESS) of the evinacumab weighted cohort was 9.9 and this decreased to 3.9 when patients receiving lomitapide were excluded. The EAG considers the main analyses to be the most suitable for decision making but is concerned by the resulting low ESSs.

Table 16. Comparison of baseline characteristics in ELIPSE before and after matching to Cuchel *et al.* 2013 (Reproduced from CS, Table 20)

Cohort	n/ESS	Age (years), mean	CHD (% yes)	LDL-C (mg/dL), mean
Evinacumab unadjusted	43.0	44.3	51.0	259.5
Main analysis (matching variables: age, CHD, LDL-C)				
Evinacumab weighted	9.9	30.7	72.0	336.4
Lomitapide	29.0	30.7	72.0	336.4
Sensitivity analysis (matching variable: age)				
Evinacumab weighted	23.6	30.7	NA	NA
Lomitapide	29.0	30.7	NA	NA

Abbreviations: CHD, coronary heart disease; dL, decilitre; ESS, effective sample size; LDL-C, low-density lipoprotein cholesterol; mg, milligram; n, sample size; NA, not applicable.

3.4.4 *Clinical effectiveness results of MAIC versus lomitapide*

The results of the MAIC for mean difference in percentage change in LDL-C from baseline for evinacumab compared with lomitapide are reported in Table 17. In the MAIC (adjusting for age, CHD and LDL-C), where patients receiving background lomitapide in ELIPSE were included, evinacumab was associated with a numerically larger reduction in LDL-C compared with lomitapide (mean difference evinacumab versus lomitapide: -14.98%). The MAIC adjusting for age, CHD and LDL-C, and excluding patients receiving background lomitapide from the evinacumab arm of ELIPSE resulted in a mean difference of 6.27 for the comparison of evinacumab versus lomitapide, and thus suggests a numerically greater reduction in LDL-C with lomitapide. The EAG notes that neither MAIC where age, CHD, and LDL-C were matched, demonstrated a statistically significant difference ($p<0.05$) between evinacumab and lomitapide (Table 17).

The EAG considers the MAIC excluding the patients on lomitapide in the evinacumab arm of ELIPSE to be more consistent with the company's positioning of evinacumab in the treatment pathway compared to the MAIC including lomitapide patients in the evinacumab arm. The EAG also notes that when excluding patients on background lomitapide from the MAIC, the ESS is only 3.9 for the main MAIC (adjusted for age, CHD and LDL-C) and when the lomitapide patients are included the ESS is 9.9; both therefore comprise small ESSs. The EAG considers the results from the MAICs to be uncertain, principally due to poor matching between the studies, which is exacerbated by the limited reporting of baseline characteristics from Cuchel *et al.* 2013 and the small number of patients included in each study. However, the EAG considers that it would not be unreasonable to interpret the results as a lack of evidence to suggest a substantial difference in LDL-C reduction with evinacumab and lomitapide.

Table 17. Results of the MAIC for mean difference in percentage change in LDL-C from baseline for evinacumab vs. lomitapide (adapted from CS Table 21 and CQ response appendix for question A16).

Method	Matching variables	Evinacumab n/ESS	Lomitapide n	Mean (95% CI) evinacumab	Mean (95% CI) lomitapide	Mean Difference (95% CI) evinacumab vs lomitapide
Including patients receiving lomitapide						
Unadjusted Naïve ITC	NA	43.0	29.0	-47.24 (-56.18 to -38.31)	-40.1 (-51.47 to -28.73) [a]	-7.14 (-21.91 to 7.63)
MAIC	Age, CHD, LDL-C	9.9	29.0	-55.08 (-71.90 to -38.27)	-40.1 (-51.47 to -28.73) [a]	-14.98 (-36.76 to 6.80)
MAIC (sensitivity analysis)	Age	23.6	29.0	-56.40 (-64.66 to -48.14)	-40.1 (-51.47 to -28.73) [a]	-16.3 (-30.72 to -1.88)*
Excluding patients receiving lomitapide						
Unadjusted naïve ITC	NA	32.0	29.0	-46.42 (-57.62 to -35.23)	-40.1 (-51.47 to -28.73) [a]	-6.32 (-22.7 to -9.63)
MAIC	Age, CHD, LDL-C	3.9	29.0	-33.83 (-96.84 to 29.17)	-40.1 (-51.47 to -28.73) [a]	6.27 (-26.1 to 38.64)
MAIC (sensitivity analysis)	Age	16.7	29.0	-54.94 (-65.16 to -44.72)	-40.1 (-51.47 to -28.73) [a]	-14.84 (-30.08 to 0.4)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; ESS, effective sample size; ITC, indirect treatment comparison; LDL-C, low-density lipoprotein cholesterol; MAIC, matching-adjusted indirect comparison; n, number of patients.

[a] Data presented to no decimal places to reflect the reporting style by Cuchel *et al.* 2013.

*Evinacumab was statistically superior to lomitapide when the evinacumab cohort was matched for age.

3.5 Conclusions of the clinical effectiveness section

The EAG considers the key evidence submitted by the company in support of the clinical efficacy and safety of evinacumab for treating HoFH to be the double-blind treatment period from the ELIPSE[13] RCT of evinacumab versus placebo (Section 3.2.1). The EAG notes that the company has also submitted supportive evidence from single-arm studies with the key single-arm trial data comprising an interim analysis of Study R1500-CL-1719[10, 27]: a single-arm, open-label, long-term study on the safety and efficacy of evinacumab with a planned follow up of up to 192 weeks (Section 3.2.2). The EAG considers the ELIPSE trial to align well with the NICE final scope in terms of intervention and outcomes but considers there to be potential limitations in relation to its generalisability to the UK HoFH population (Section 2.3.1).

The EAG is concerned about the low proportion of adolescents enrolled in the ELIPSE trial (n=2) and that the background LLT and LDL apheresis usage in ELIPSE may not be representative of the treatments currently used in England for HoFH (Section 2.3.1). The EAG notes that evinacumab has marketing authorisation in England for use in people aged 12 and over, and that the NICE final scope specified the population to also include those aged 12 years and over with HoFH. However, the EAG is concerned that the clinical effectiveness data for adolescents in ELIPSE is limited due to the inclusion of only 2 patients aged <18 years. The EAG notes that there are data for [redacted] patients from the interim analysis of the long-term, single-arm Study R1500-CL-1719, but also notes that these are non-comparative data. In addition, there is no analysis of cost-effectiveness presented in the CS for the adolescent population. As discussed in Section 3.3.4.1, [redacted] in the adolescent population with appropriately adjusted baseline characteristics and inputs for an adolescent population in the economic model.

In terms of background LLT and LDL apheresis usage in ELIPSE, the EAG's clinical experts reported that statin (93.8% in ELIPSE), ezetimibe (75.4%) and LDL apheresis (33.8%) usage maybe higher in the UK. In addition, the EAG notes 25.1% of patients were on lomitapide as a background LLT a baseline in ELIPSE and that lomitapide is the key comparator considered in the company submission. In addition to lomitapide being a comparator for adults, the EAG considers that continuation of maximally tolerated background LLTs (including LDL apheresis where appropriate) in the adolescent population; and continuation of maximally tolerated background LLTs (including LDL apheresis where appropriate) in the adult population unsuitable for lomitapide are comparators of relevance based on the company's restricted positioning of evinacumab in the HoFH treatment pathway. The EAG does not consider either of these two additional comparisons to have been formally presented in the CS but does consider the data from ELIPSE trial could be used to inform analyses of clinical and cost-effectiveness for the comparison of evinacumab versus continued maximally tolerated LLT.

The primary efficacy outcome of the ELIPSE trial was the percent change in calculated LDL-C from baseline to week 24, and evinacumab demonstrated a statistically significant reduction in LDL-C versus placebo with a least squares (LS) mean difference of -49.0% (95% CI: -65% to -33.1%; p<0.001

for evinacumab versus placebo [Figure 2]). The EAG also notes that during the double-blind treatment period (DBTP) of ELIPSE there were no TEAEs leading to death or discontinuation of study treatment, and the two SAEs in the DBTP were not deemed to be related to evinacumab, the study drug (Section 3.3.5).

The EAG notes that there is an absence of head-to-head data comparing evinacumab with lomitapide and that the company has conducted an MAIC to enable a comparison between the two drugs. The EAG is concerned that 25.6% of patients in the evinacumab arm of ELIPSE received background therapy with lomitapide (n=11), which could potentially confound the results of the MAIC. In addition, the EAG notes that LDL apheresis usage was much higher in Cuchel *et al.* compared to in the evinacumab arm of ELIPSE (62.1% versus 32.6%, respectively) and Cuchel *et al.* did not include patients on PCSK9 inhibitors because the study was conducted prior to the introduction of PCSK9 inhibitors into routine clinical practice for HoFH. The EAG is particularly concerned about the comparability and relevance of the findings in Cuchel *et al.* to clinical practice today given the lack of patients on PCSK9 inhibitors in the study, and considers it to be unknown what impact this has on the results of the MAICs. However, the EAG notes that in the discussion section of the study publication for Cuchel *et al.* it is reported that the percentage reduction in LDL-C was "*similar to that observed during lomitapide monotherapy in HoFH patients"* from another publication,[35] and this therefore suggests lomitapide has similar efficacy when added to existing background LLTs.

The EAG requested the company provide results of an MAIC excluding the patients on lomitapide in the evinacumab arm and this resulted in a decrease in the ESS for the main analysis, when all the matching variables were applied, from 9.9 to 3.9. The EAG considers the main MAIC analyses with adjustment for all variable possible to be the most suitable for decision making, and that the MAIC excluding the patients on lomitapide in the evinacumab arm of ELIPSE is more consistent with the company's positioning of evinacumab in the treatment pathway; nevertheless, the EAG is concerned by the resulting low ESSs. The EAG also considers the results from the MAICs to be uncertain, principally due to poor matching between the studies, which is exacerbated by the limited reporting of baseline characteristics from Cuchel *et al*. 2013 and the small number of patients included in each study. However, the EAG considers that it would not be unreasonable to interpret the results as a lack of evidence to suggest a substantial difference in LDL-C reduction with evinacumab and lomitapide.

In summary, the EAG is concerned that continuation of background LLT without lomitapide is a potentially relevant comparator for both the adult and adolescent populations (Section 2.3.3), and that this has not been considered in cost-effectiveness analyses presented in the CS. Additionally, the EAG is concerned that there is a lack of robust clinical data to enable a robust comparison of evinacumab with any of the relevant comparator treatments, and therefore any estimates of clinical efficacy should be interpreted with caution.

4 Cost effectiveness

Table 18 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case results.

As outlined in Section 2.3.3, the EAG considers that continuation of LLTs (lipid lowering therapies) are also comparators of interest. Results of the analyses comparing evinacumab to continuation of LLTs are provided in Section 6.3.

Table 18. Company's updated base case results (post-clarification)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Lomitapide	5,976,577	12.84	10.05	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Lomitapide	6,029,571	12.96	10.12	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

4.1 EAG comment on the company's review of cost effectiveness evidence.

The company carried out three systematic literature reviews (SLRs) to identify published studies that could inform the cost-effectiveness evaluation of evinacumab. These SLRs covered the cost-effectiveness evidence, the health-related quality of life (HRQoL) evidence and the costs and resource use evidence associated with homozygous familial hypercholesterolaemia (HoFH), not limited by intervention. Searches were initially conducted in October and November 2020 and two updated searches were run in February and March 2023. A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 19. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 19. EAG's critique of company's systematic literature review

Systematic literature review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G1.1.3	Appendix H.1.1	Appendix I.1.1	Appropriate

Inclusion/ exclusion criteria	Appendix G1.2.2	Appendix G1.2.2	Appendix G1.2.2	Appropriate
Screening	Appendix G1.2.1	Appendix G1.2.1	Appendix G1.2.1	Appropriate
Data extraction	No studies were found to be relevant for inclusion.	Appendix H.3 (No appropriate studies identified)	Appendix I.1.3 (No appropriate studies identified)	Appropriate. (No appropriate studies identified)
Quality assessment of included studies	N/a	None conducted.	None conducted	The company explained in their clarification response to question B42 that NICE guidance does not stipulate the use of critical appraisal tools for HRQoL and costs study types. However, the EAG does not consider this an issue as none of the identified studies were deemed suitable for inclusion in the economic model.

Abbreviations: CS, company submission; EAG, evidence review group; HRQoL, health related quality of life; N/a, not applicable.

Overall, the company's SLRs did not identify any relevant cost-effectiveness studies, HRQoL studies or cost and resource use studies. Instead, the company used published studies, including NICE technology appraisals in related disease areas (such as heterozygous familial hypercholesterolaemia) to aid development of the *de novo* cost-effectiveness for evinacumab for the treatment of HoFH. The *de novo* cost-effectiveness model is described in Section 4.2.4.

4.2 Summary and critique of company's submitted economic evaluation by the EAG.

4.2.1 NICE reference case checklist

Table 20 summarises the EAG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 20. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The major health effects for patients with HoFH aged 18 and older have been included in the economic model. While revascularisation was included in

		the final scope it was not explicitly included in the model.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis has been provided by the company with fully incremental analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime horizon (100 years of age).
Synthesis of evidence on health effects	Based on systematic review	The company has performed an appropriate systematic review.
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.	Health outcomes have been expressed in terms of QALYs, with health state utility values being informed by Ara and Brazier 2010, based on EQ-5D published data for CV events in the general population[36]. This is preferred due to the severely limited published EQ-5D HoFH specific literature available.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D values obtained from the ELIPSE trial were not used in the model. Instead, health state utility values were informed using NICE TA694 and TA385 which are based on values published by Ara and Brazier 2010 and are not specific to HoFH patients.[37, 38]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The sources considered for HRQoL can be considered relevant to the UK, however they are not HoFH specific.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.
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	Costs included in the analysis have been sourced using NHS reference costs, PSSRU, BNF, eMIT and the NHS Drug tariff.[39, 40]
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects.

Abbreviations: EAG, External Assessment Group; NHS, national health service; HoFH, homozygous familial hypercholesterolaemia; HRQoL, health related quality of life; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Intervention and comparators

The intervention considered in the economic model was evinacumab. In line with its marketing authorisation the dosing assumed in the model was 15mg/kg administered intravenously (IV) over 60 minutes once a month.

The company considered lomitapide the only appropriate comparator treatment to evinacumab. Lomitapide is an oral treatment, with 10-60mg taken daily depending on time on treatment and adverse events.

4.2.2.1 EAG critique

As described in Section 2.3.3, the EAG considers that the relevant comparators to be considered in this STA are:

1) lomitapide with continuation of maximally tolerated background LLTs (including low density lipid [LDL] apheresis where appropriate) in the adult population;
2) continuation of maximally tolerated background LLTs (including LDL apheresis where appropriate) in the adolescent population, and in the adult population unsuitable for lomitapide.

As the company did not provide a cost-effectiveness analysis comparing evinacumab against continuation of LLTs in the CS, the EAG has conducted this analysis. Results of this additional analysis are provided in Section 6.3.

4.2.3 Population

The HoFH population considered in the economic model are patients who have not achieved target low-density lipoprotein-cholesterol (LDL-C) concentrations of 1.8 mmol/L on current lipid lowering therapies (LLTs) which include statins, ezetimibe, a PCSK9 inhibitor (evolocumab) and LDL-apheresis.

Patient starting age, body mass index, weight and sex distribution in the model was 42 years old, 25.6, 73kg and 54% female, reflecting the mean age and patient characteristics of the ELIPSE trial. Similarly, 32% of patients were assumed to have the null/null mutation as was measured in ELIPSE.

In the company's base case, all patients entering the model are assumed to have no CV event history and therefore are considered primary prevention patients.

The patient baseline LDL-C assumed in the model was informed using a UK based HoFH retrospective study by Thompson *et al.* Baseline LDL-C from Thompson *et al*.[1] was adjusted to the background LLT treatments from the ELIPSE study, as described in Section 4.2.7.1, resulting in baseline LDL-C of 7.93mmol/L in the model.

4.2.3.1 EAG critique

The EAG considers that patient characteristics from ELIPSE have been properly used to inform the economic model, aside from the company's assumption of no CV event history at baseline. The EAG also disagrees with the use of the Thompson *et al.* study to estimate patient baseline LDL in the model and discusses the issue in detail in Section 4.2.7.1.

The EAG's clinical experts expressed a consensus of opinion that many HoFH patients are likely to experience CV events before 42 years of age. Evidence for this can be seen in the patient characteristics outlined in Table 10 in the CS in which 52.3% of patients had a history of coronary heart disease (CHD) in ELIPSE. Of the 52.3% with a CHD history, 18.5% had experienced an acute myocardial infarction, 30.8% had angina (chronic stable or unstable) and 41.5% had a coronary revascularisation procedure. Therefore, the EAG considers that a model consisting of only primary prevention HoFH patients is not reflective of UK HoFH patients, or the population in the ELIPSE trial.

At the clarification stage the EAG requested that the company updated their base case approach to include both primary prevention (no history of CVD) and secondary prevention (those with a history of CV events) patients in the model, according to their baseline characteristics from ELIPSE. Primary prevention patients would still enter the model in the stable HoFH health state while secondary prevention patients would be distributed among the post-event health states according to baseline history of disease from ELIPSE where possible. The company partially complied with the EAG's and conducted a scenario analysis where 50% of patients entered the model in the stable HoFH health state as primary prevention patients and 50% were distributed to post-event health states as secondary prevention patients.

The EAG notes that the company's scenario analysis is based on a simplification of fully capturing the impact of having a secondary (as well as primary) prevention population at baseline - the company's scenario assumed that the utility values associated with acute secondary events (i.e. for secondary prevention patients) is the same as primary prevention patients experiencing a first acute event and moving to a post-event health state. In Section 4.9.2.1 the EAG discusses the issue further

and presents a comparison of the utility values for patients with a history of CV disease and the utility values used in the model, based on data from Ara and Brazier (2010).[36]

Furthermore, the company was also requested to consider the cost difference between primary and secondary events. The company stated that as costs were obtained from Danese *et al.* (2016), which combined costs across both primary and secondary events, the scenario was not conducted. However, as noted in EAG report for TA694, first and second event costs from Danese *et al*., 2016 are generally consistent and so in terms of estimating total costs for the model, it is unlikely to make a substantial difference in the final economic results.

Given that the majority of the ELIPSE patients were secondary prevention patients and the EAG's clinical experts' opinion that secondary prevention patients in the UK may be closer to 70%, the EAG recommends that the company conducts the analysis requested by the EAG at clarification, where the impact of having a secondary prevention population at baseline in the model is fully captured in terms of QALYs and costs.

While the company has not justified the assumption that 50% of patients would be primary prevention patients at 42 years old, this proportion appears reflective of patients in ELIPSE with any incidence of myocardial infarction, angina or revascularisation at baseline (52.3%). The EAG notes that in ELIPSE, 90.8% of patients were reported to have a cardiovascular history or a risk factor across both treatment arms at baseline. The EAG is unclear how risk factors were classified at baseline in the trial, however, notes that clinical expert opinion provided to the EAG was that approximately 70% of HoFH patients will have a history of CV events at 42 years. Therefore, the EAG ran a scenario analysis similar to the company's scenario analysis where 70% of patients entered the model as secondary prevention patients. For the reasons previously described, the EAG does not consider that scenario capture the full health outcomes associated with secondary prevention patients due to the limitations of the model.

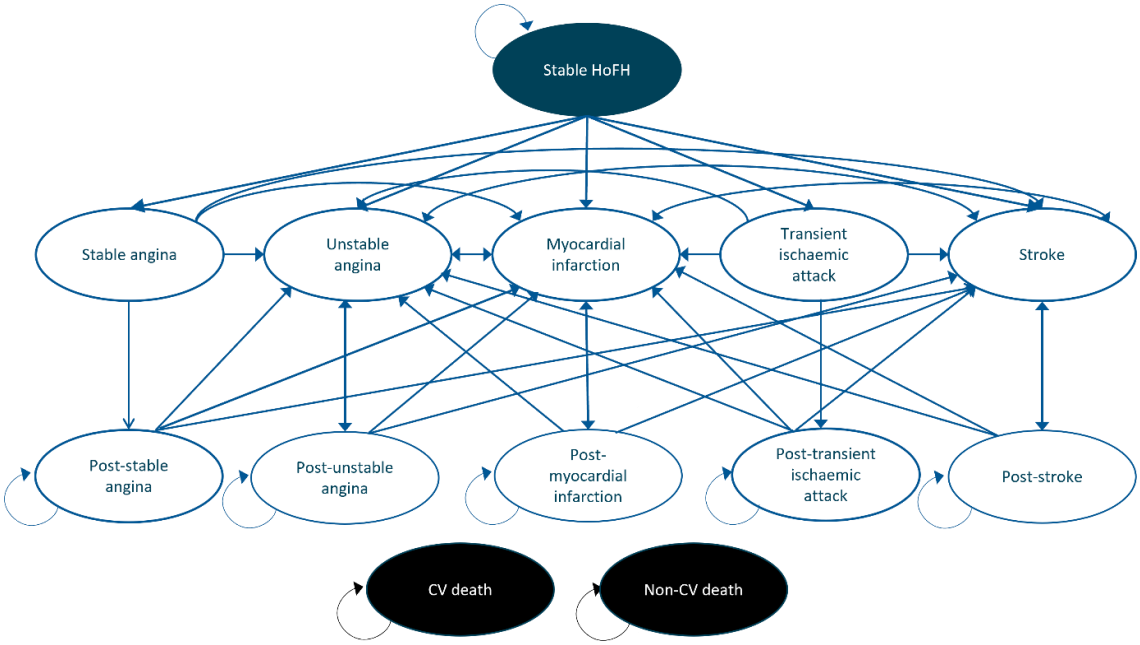
The EAG notes that although adult and adolescent patient populations are considered separately in the NICE final scope for evaluation, they are not considered separately in the model. Instead, the model cohort is reflective of the total ELIPSE study population, of which only two patients were between 12 and 18 years old. As such, the cost-effectiveness analysis presented by the company and the scenarios conducted by the EAG only applies to adults and is not generalisable to the adolescent population.

In the EAG's cost-effectiveness analysis comparing evinacumab to the continuation of LLTs, the population and baseline LDL-C considered was that of ELIPSE. It important to highlight that the ELIPSE data includes some patients on background lomitapide but the EAG considers that including these patient in the analysis avoids the need to break randomisation and thus results in a more robust analysis. Therefore, the EAG has not controlled for patients also treated with lomitapide. At clarification the company was asked to provide the LDL-C baseline for the patients not treated with lomitapide, however the company did not provide this data.

In the EAG's cost-effectiveness analysis comparing evinacumab to lomitapide, the population and baseline LDL-C assumed were also from ELIPSE. While the MAIC calculated a base line LDL-C of 8.9 mmol/L the EAG considers that baseline LDL-C from ELIPSE is more representative of UK HoFH patients for the reasons as described in Section3.4.4.

4.2.4 Modelling approach and model structure

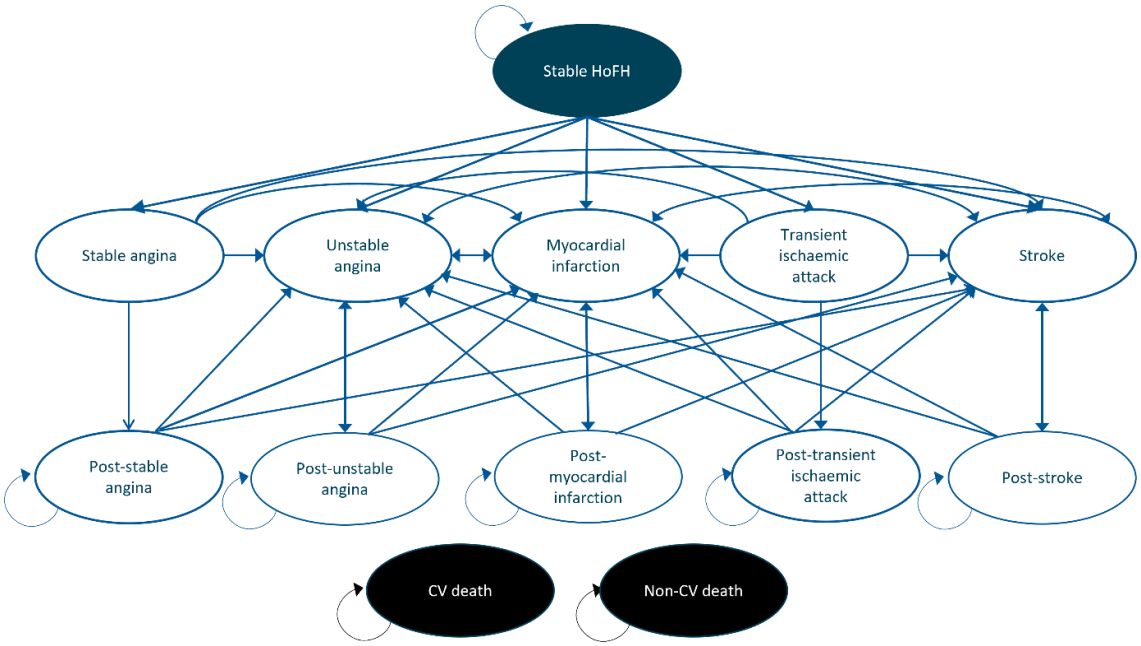
To model the epidemiology of hypercholesterolaemia in HoFH patients and assess the cost-effectiveness of treatments, the company developed a *de novo* Markov model in Excel®. The company states that the structure of the model was similar to that of previous NICE HTA submissions for hypercholesterolaemia, such as NICE TA694 and TA385[37, 38], which both utilise a model structure informed by Ara *et al.* (2008)[41]. The model schematic and the description of health states are outlined in Figure 10 and Figure 10. Schematic representation of cost-effectiveness model. Reproduced from Figure 24 in the CS.



Abbreviations: CV, cardiovascular; HoFH, homozygous familial hypercholesterolemia.

Table 21.

Figure 10. Schematic representation of cost-effectiveness model. Reproduced from Figure 24 in the CS.



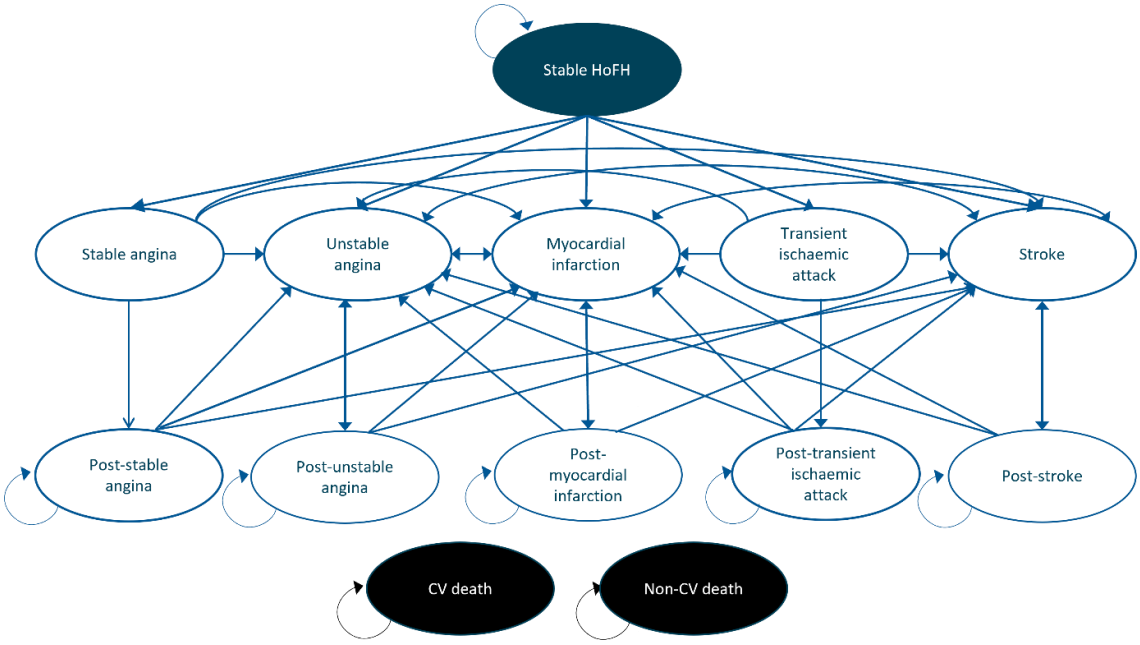
Abbreviations: CV, cardiovascular; HoFH, homozygous familial hypercholesterolemia.

Table 21. Description of health states in the model. Reproduced from Table 28 in the CS.

Health states	Definition
Stable HoFH	No previous history of CV events
Stable angina	First occurrence of angina that only occurs during physical exertion
Post-stable angina	Patients whose stable angina began more than a year ago
Unstable angina	Occurrence of a form of acute coronary syndrome. An episode of angina that occurs randomly or unpredictably, including at rest
Post-unstable angina	Patients whose first episode of unstable angina was more than a year ago
MI	Non-fatal myocardial infarction. A form of acute coronary syndrome with permanent sequalae
Post-MI	Patients whose MI occurred more than a year ago
TIA	Transient ischaemic attack
Post-TIA	Patients whose TIA occurred more than a year ago
Stroke	Non-fatal ischaemic stroke
Post-stroke	Patients whose stroke occurred more than a year ago
CV death	Death due to any CV events
Non-CV death	Death due to any non-CV cause

Abbreviations: CV, cardiovascular; MI, myocardial infarction; TIA, transient ischemic attack.

As described in Figure 10 and Figure 10. Schematic representation of cost-effectiveness model. Reproduced from Figure 24 in the CS.



Abbreviations: CV, cardiovascular; HoFH, homozygous familial hypercholesterolemia.

Table 21 non-fatal CV events were split into two health states, the acute and the post-event. The acute health state corresponds to an acute phase, accounting for the cost and HRQoL impact in the first year following an event, while the post-event phase allows for the longer-term outcomes associated with each event to be considered separately.

In the company's base case, patients enter the model in the stable HoFH health state and are considered to have no CV event history. From the stable HoFH health state, patients can transition to any of the five acute event health states, namely; stable angina (SA), unstable angina (UA), myocardial infarction (MI), transient ischaemic attack (TIA), stroke. Once a patient has progressed to an acute event health state, patients are able to transition to either the post-event health state of their current acute event or to experience an alternative acute event. From any health state, patients can transition to the death state, which incorporates both cardiovascular mortality (CVM) and all-cause mortality (ACM). Patients could not remain in the same acute health state for more than one cycle (one year) and could only transition to the SA or TIA health states from the stable HoFH state.

The company highlighted that although patients in the model can only experience one event per year (i.e., one model cycle), in clinical practice patients may experience multiple non-fatal CV events within a year and suffer health consequences from more than one health state at a time. Therefore, the model makes a simplifying assumption that a patient's healthcare resource use and HRQoL are dictated by their most recent annual CV event to avoid the complexity of all possible combinations and sequences of CV events.

The source of the clinical data included in the model are summarised in Table 22.

Table 22. Summary of clinical data included in the economic model.

Parameter	Description	Section
Baseline LDL-C	Informed by Thompson *et al.*,[1] adjusted to reflect background treatment mix in ELIPSE	4.2.7.1
Baseline CV risk		
Time to CV death	Informed by Thompson *et al.*,[1] extrapolated using the Gompertz curve.	4.2.6
Baseline distribution of CV events	Thompson *et al.*,[1] and Ward *et al.*(2007)[42]	
Treatment efficacy		
Reduction in LDL-C for evinacumab and lomitapide	MAIC of ELIPSE (evinacumab) and Cuchel *et al.* (lomitapide)[16]	4.2.7.1
Relationship between LDL-C and CV risk	CTTC meta-analysis[43]	4.2.7.3
Risk of future CV events		
Probability of recurrent events	Ward *et al.* [42]	4.2.8
Abbreviations: CV, cardiovascular; LDL-C, low-density lipoprotein-cholesterol.		

4.2.4.1 EAG critique

During clarification, the EAG requested that the company conducted a scenario analysis to assess the impact of patients being able to experience multiple CV events on patients' quality of life and costs. The company did not conduct the analysis requested as by the EAG and justified their decision by stating that the model structure does not contain health states for multiple events, therefore the analysis could not be undertaken. The EAG notes the company's model is a simplification, and that accounting for multiple CV events in the same model cycle would have benefited the most effective treatment in the model.

At the clarification stage the EAG also requested that the company updated their base case approach to include both primary prevention (no history of CVD) and secondary prevention (those with a history of CV events) patients in the model, according to their baseline characteristics from ELIPSE. As discussed in Section 4.2.3.1, the EAG notes that the company's scenario analysis was limited with regards to capturing the impact of having a secondary (as well as primary) prevention population at baseline, particularly on patients' quality of life. Given that the majority of the ELIPSE patients were secondary prevention patients and the EAG's clinical experts' opinion that secondary prevention patients in the UK may be closer to 70%, the EAG recommends that the company conducts the analysis requested by the EAG at clarification, where the impact of having a secondary prevention population at baseline in the model is fully captured in terms of QALYs and costs.

Furthermore, the EAG notes that in similar NICE indications for hypercholesterolaemia (TA694 and TA385)[37, 38], acute coronary syndrome and revascularisation were also considered as events in the model, and that revascularisation was included in the NICE final scope for this submission.[44] At clarification when the company was asked why these events had not been considered in the model structure, the company responded that it was assumed that where revascularisation is urgent and undertaken following a CV event, the impact of revascularisation was captured within the costs and utility data for those health states. Similarly for acute coronary syndrome, the company considered that this event is captured by the cardiac events represented in the economic model.

While the company has clearly outlined which transitions are possible between health states and the logic behind why some transitions are not possible (such as remaining in the same acute event health state for more than one cycle). When questioned at clarification why patients can only transition to the TIA and SA health states from the stable HoFH health state, the company stated that the model was built to avoid health state utility values (HSUV's) increasing when transitioning to a less sever health state. The EAG considers that the rationale provided by the company is insufficient given that SA is associated with the same HSUV as UA, with these utilities being lower than the post-event health states. As such, if patients are able to move from post-event health states to UA, given this is considered a progression of disease within the model, the same logic would allow patients to transition to the SA health state. The EAG notes that a similar issue was raised in a NICE TA694,[37] however the inclusion of patients' transition to the SA health state had a negligible impact on the ICER, and the EAG expected the same to be true in this STA.

4.2.5 Perspective, time horizon and discounting

The model cycle length was one year (with a half cycle correction applied) and a lifetime horizon was adopted (up to age 100 years) allowing for the model to run for 58 cycles given a patient starting age of 42 years in the economic model. The perspective of the analysis was based on the UK NHS and PSS, with future costs and benefits discounted using an annual rate of 3.5%, as per the NICE reference case.

4.2.6 Mortality

As the ELIPSE study did not capture cardiovascular mortality (CVM), the company conducted a targeted literature review to identify publications reporting CVM events over time for HoFH patients. From the identified literature, a retrospective study by Thompson *et al.* (2018)[1] was chosen to inform CVM risk in the model.

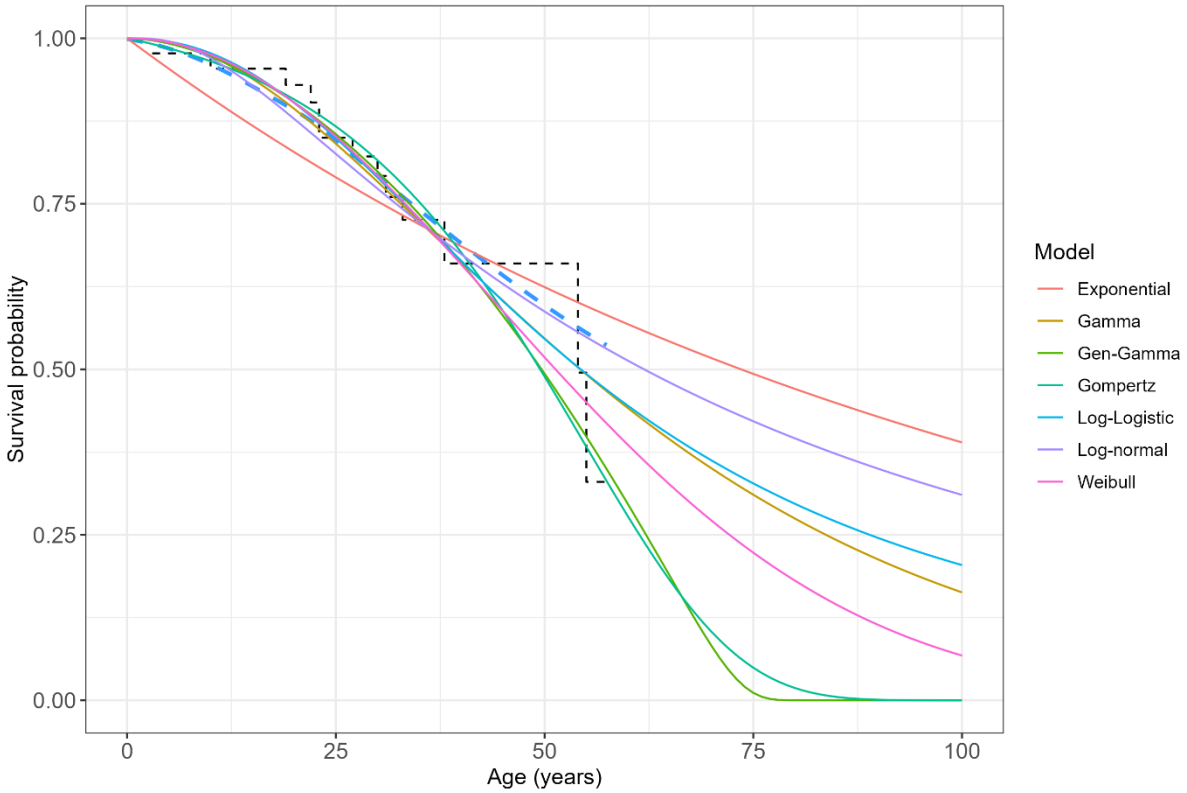
The Thompson *et al*. study included 44 UK HoFH patients referred to Hammersmith Hospital between 1964 and 2014 and reported individual patient data. Recorded patient study data included LLTs received, CV outcomes, lipid levels and genetic characteristics. Over the course of the study, 13 patients died, 30 remained alive and one was lost to follow up. Of the LLTs prescribed, 89% of patients received statins, 59% LDL-C apheresis, and 70.5% ezetimibe.

Using the CVM data from Thompson, the company modelled time to CVM using standard parametric models (exponential, Weibull, lognormal, loglogistic, Gompertz and gamma) according to NICE DSU TSD 14 (Figure 11).[45] Of these models, the Gompertz resulted in the lowest Akaike and Bayesian information criterion scores and was considered by the company to produce the most clinically plausible extrapolation leading to it being included in the base case.

All-cause mortality (ACM) was included in the model using age and sex-matched ACM values derived from up-to-date UK life tables produced by the Office for National Statistics.[46] The company notes that the ACM values were used directly from the lifetables, without adjustment for the underlying rate of CVM, which was already estimated separately in the company's model. The company justified this approach by stating that the impact of double counting CVM deaths from both the CVM and ACM estimates would be negligible.

As described in detail in 4.2.7.3, treatment effects, in terms of LDL-C reduction, reduced the risk of CVM in the model via the relationship between CVM risk and a 1 mmol/L reduction in LDL-C from the CTTC meta-analysis.[43]

Figure 11. Derived survival curves for CVM based on Thompson *et al.* Reproduced from Figure 27 in the CS.



4.2.6.1 EAG critique

The EAG considers that while the Thompson *et al.* data provides CVM estimates from HoFH patients and can be considered preferential to using general population estimates, the CVM extrapolations derived from Thompson *et al.*[1] may not be generalisable to current HoFH patients in the UK NHS due to the difference in access to treatments of those who died during the study and to current HoFH patients.

The patient profiles of those who were alive and dead by the end of the Thompson *et al.*[1] study are described as being distinctly different, with this difference being driven by the treatments available during the study and advancements in LDL apheresis efficacy. The main therapies of the 13 patients who died were plasma exchange and LDL apheresis. On average, the patients who died in the study started their treatment in 1979 and died in 1992, with statins only being granted marketing authorisation in 1998 in the UK. This meant that just over 60% of the dead patients received statin therapies with many only having access to statins much later in life. Adversely, those who were alive by the end of the study on average started treatment in 1994 and therefore had access to statins at a much younger age and for a longer period of time before the study end. Advances in the LDL apheresis techniques employed and their application also resulted in apheresis being performed more frequently and efficiently for patients alive by the end of the study. The EAG also notes that evolocumab, which 76.9% of patients were treated with in ELIPSE, was only granted marketing authorisation in the UK in 2015 and so no patients in the Thompson study received this treatment.

The average on-treatment total cholesterol (TC) for patients who died by the end of the study was 14.5 ± 6.0 mmol/L compared to those alive by the end of the study of 8.1 ± 2.8 mmol/L.

The EAG considers that those who died in the study were more at risk and received less effective treatment compared to those alive, who more accurately reflect current UK clinical practice. The inclusion of these patients in the CVM analysis is likely to confound the calculated CVM, leading to an overestimation of CVM risk over time. However, as CVM cannot be calculated from those alive by the end of the study and the EAG considers the use of HoFH specific studies preferential to those of the general population, the EAG has not suggested the use of an alternative CVM dataset to inform the model.

In the company's sensitivity analysis, incremental costs and QLAYs when comparing evinacumab to lomitapide were sensitive to both the CVM rate and shape in the economic model. When considering the lower confident interval of CVM rate, as Thompson *et al.*[1] conversely is likely to overestimate CVM given the inclusion of the less well treated patient group, the incremental QALYS were reduced by 0.08 and the incremental costs increased by approximately one million pounds, with the ICER remaining dominant. The EAG considers that additional sensitivity analysis using lower risks of CVM would reduce the uncertainty introduced by the CVM from Thompson *et al.*[1]

4.2.7 Treatment effectiveness

In the company's economic model, all treatment effects are applied by calculating the LDL-C reduction associated with treatments compared to baseline LDL-C.

4.2.7.1 Calculating baseline LDL-C and treatment efficacies

As the Thompson *et al.*[1] study was used by the company to inform the CV risk profile in the model, the company chose to inform baseline LDL-C in the model also using the Thompson *et al.* study[1], adjusting to the difference in treatments used in ELIPSE, which was considers more representative of current clinical practice.

As Thompson *et al.*[1] only recorded pre-treatment LDL-C, and not on-treatment LDL-C. The company used the pre- and post-treatment total cholesterol (TC) and assumed the difference in TC levels was directly due to the treatment effects on LDL-C. Where pre-treatment TC values were missing, the company estimated patient values using a linear regression informed by the 27 sets of pre and on-treatment TC data available. From the 39 patients in Thompson *et al.*[1] from which pre- and post-treatment TC was available or could be derived, baseline LDL-C was calculated at 8.71 mmol/L.

Given the difference in background LLTs between Thompson *et al*.[1] and ELIPSE (Table 23), the company adjusted the baseline LDL-C from Thompson *et al.* to reflect the background treatments given in ELIPSE, which the company considered representative of the target population for this evaluation.

To achieve this the company estimated the treatment effects of all LLT background treatments individually (Table 24) and calculated the difference in the proportion of patients on specific treatments in Thompson *et al.*[1] and ELIPSE. Treatment effects were then subtracted from the Thompson *et al.*[1] LDL-C baseline where the difference in the proportion of treatments between Thompson *et al.*[1] and ELIPSE was negative and added where the difference was positive.[1] For the proportion of patients with the null/null mutations the treatment effects of statins and evolocumab were not applied.

Treatment effects of background treatments were identified using several indirect treatment comparisons (described in Section 3.4) to estimate the treatment effect of evinacumab; lomitapide; and apheresis (among others) on LDL-C baseline levels.

Using this method, from the Thompson *et al.* LDL-C baseline of 8.71 mmol/L, a baseline of 7.93 mmol/L was calculated when adjusting for the different in background LLT treatments between Thompson *et al.* and ELIPSE.[1] In the company's base case, LDL-C reductions from baseline were calculated at -4.367 mmol/L and -3.179 mmol/L respectively when using the evinacumab and lomitapide treatment effects from the MAIC.

Table 23. Difference in patient treatments between ELIPSE and Thompson *et al.*[1] studies and assumed patient treatments in the model.

Treatment	Proportion of patients on treatments in study		Difference in treatment mix	Proportion of patients on treatments in the model	
	ELIPSE study cohort	Thompson *et al.* (2015)		Evinacumab arm	Lomitapide arm
Atorvastatin	93.8%	88.6%	5.2%	93.8%	93.8%
Ezetimibe	75.4%	70.5%	4.9%	75.4%	75.4%
Evolocumab	76.9%	0%	76.9%	76.9%	76.9%
LDL- apheresis	33.8%	59.1%	-25.2%	33.8%	33.8%
Lomitapide	21.5%	0%	21.5%	0%	100%
Evinacumab	66%	0%	66%	100%	0%

Abbreviations: LDL, low-density lipoprotein cholesterol.

Table 24. Efficacy of interventions used in the model. Reproduced from Table 36 in the CS

Treatment	LDL-C efficacy	Source
Atorvastatin	-20.0%	SPC, clinical trial.[47]
Ezetimibe (10 mg)	-20.7%	MAIC Same value as RCT from Gagne *et al.* (2002). [18]
Evolocumab (420 mg monthly)	-30.8%	Bucher's ITC. Original data from TESLA B.[19]
Lomitapide	-40.1%	MAIC. Same value as ITT data from Cuchel *et al.* (2013).
LDL apheresis	-30.7%	Retrospective cohort study.
Evinacumab	-55.1%	MAIC. Original data from ELIPSE.

Abbreviations: ITC, indirect treatment comparison; LDL-C; low-density lipoprotein cholesterol; MAIC, match adjusted indirect comparison; SPC, summary of product characteristics

4.2.7.2 EAG critique

The EAG considers that the company's approach to calculating baseline LDL-C in the model, by adjusting the baseline from Thompson *et al.*[1] by the difference in background LLTs in ELIPSE, introduces unnecessary uncertainty and lacks methodological robustness.

Compared to the 6.7mmol/L baseline LDL-C and 3.48 mmol/L LDL-C reduction recorded in ELIPSE for patients treated with evinacumab, the model estimates a baseline LDL-C of 7.93mmol/L and a reduction of 4.367 mmol/L LDL-C. An overestimation of 18% and 25% respectively. As such the EAG considers the company's approach a key issue.

When comparing evinacumab to lomitapide, the EAG considers that applying the treatment effects from the unanchored MAIC as described in Section 3.4.3 to the baseline LDL-C from ELIPSE (without any further adjustment) would have provided more robust estimates of LDL-C. At clarification the company was requested to conduct a scenario analysis using this approach, which the company did not provide. As an explanation for why the scenario was not conducted, the company stated that efficacy of treatments should be considered independent of background treatments received and that it would be inappropriate not to adjust for background treatment differences given that the ELIPSE treatment mix is more representative of UK clinical practice than Thompson *et al.* [1]

The EAG agrees with the company that the ELIPSE treatment mix is more reflective of UK clinical practice than Thompson *et al.*[1] and for the same reason does not agree with the use of Thompson *et al.*[1] to estimate the baseline LDL-C. The ELIPSE values inherently include the LLT background treatment effects to which the MAIC values can be applied and so no further adjustment for background LLTs are required.

As the MAIC treatment effects used in the company base case included lomitapide treated patients in the evinacumab arm, the EAG conducted a scenario removing these patients. While the treatment effects for lomitapide remained the same -40.1% (95% confidence interval of -51.47% to 28.73%), the treatment effects for evinacumab were reduced from -55.08% to -33.83% (95% confidence interval of -96.84% to 29.17%). Results of the scenarios are outlined in Section 6.3. The EAG therefore considers the results from the MAICs to be uncertain but overall considers the MAIC excluding the patients on lomitapide in the evinacumab arm of ELIPSE to be more consistent with the company's positioning of evinacumab in the treatment pathway and is preferred in the EAG's base case when comparing evinacumab to lomitapide.

The EAG notes that while a baseline LDL-C was also calculated from the MAIC (Section 3.4.4), this is unlikely to be generalisable to UK treated HoFH patients given the difference in treatments between ELIPSE and the Cuchel *et al.*[16] study to which ELIPSE was matched for the reasons described in Section 3.4.3. As such, the MAIC treatment effects were applied to the ELIPSE baseline LDL-C.

Given the uncertainty in the different MAICs conducted, the EAG considers that there is no robust evidence to indicate that evinacumab is more or less effective than lomitapide. As such the EAG has conducted an exploratory cost-minimisation analysis assuming equivalent efficacy between evinacumab and lomitapide

In the cost-minimisation scenario, the company equated the evinacumab and lomitapide efficacies to a 50% reduction in LDL-C, with the results clearly outlining evinacumab as the more cost saving treatment (Table 25). The EAG considers that the scenario should have equated treatment efficacies to either evinacumab or lomitapide and not a 50% reduction, however the results of the scenario show that evinacumab is cost saving. The EAG notes that lomitapide has an agreed patient access scheme (PAS) discount and the results of the company's cost-minimisation scenario with the lomitapide PAS is included in the confidential appendix.

Table 25. Cost minimisation scenario results.

Outcomes	Technology		Incremental
	Evinacumab + SoC	Lomitapide + SoC	
Base-case cost results			
Drug costs	[redacted]	[redacted]	[redacted]
Monitoring costs	£1,875	£1,829	£46
Health state costs	£14,119	£14,198	£-79
CV death costs	£-2,801	£-2,914	£113
Total costs	[redacted]	[redacted]	[redacted]
Cost results assuming equal efficacy			
Drug costs	[redacted]	[redacted]	[redacted]
Monitoring costs	£1,860	£1,860	0
Health state costs	£14,145	£14,145	0
CV death costs	£-2,837	£-2,837	0
Total costs	[redacted]	[redacted]	[redacted]

Abbreviations: CV, cardiovascular; SoC, standard of care.

In the EAG's scenario analysis comparing evinacumab to a continuation of background LLTs, an LDL-C baseline of 6.7 mmol/L, evinacumab LDL-C reduction of -3.48 mmol/L and LLT LDL-C increase of 0.007 mmol/L was assumed, as was measured in ELIPSE (Figure 14 in the CS).

The EAG notes there is a difference in the evinacumab treatment effects when comparing evinacumab to lomitapide or to a continuation of LLTs, with the former using the results of the MAIC and the latter the ELIPSE trial results. From the MAIC, evinacumab LDL-C reduction was calculated at -40.1% and -33.83% when adjusting for the lomitapide treated evinacumab patients, while the evinacumab LDL-C reduction from ELIPSE was calculated at -47.1%.

4.2.7.3 Translating LDL-C reduction into reduced risk of CV events in the model

To translate LDL-C reductions (described in the previous subsection) into a reduced risk of CV events, the company used a CTTC meta-analysis which established a relationship between a 1mmol/L reduction in LDL-C and a reduced risk of CV events (Table 26). [43] The LDL-C reduction and CV risk relationship outlined in the CTTC meta-analysis was calculated using the results of 26 trials studying the use of statins in approximately 170,000 study participants with atherosclerotic CVD. The CTTC meta-analysis was chosen instead of a HoFH specific approach as the company was unable to identify sufficient evidence to directly formulate an equation specifically for HoFH populations. Within the model, CV event hazards were adjusted based on a change in LDL-C according to Equation 1 below.

Equation 1. Relationship between CV event rate and LDL-C change.

$$r_{1,i} = r_{0,i}\left[\alpha_i^{(L_0 - L_1)}\right]$$

Where:
L_0 is the baseline LDL-C level in mmol/L
L_1 is the reduced LDL-C level in mmol/L
$r_{0,i}$ is the one-year rate for experiencing event i at the baseline LDL-C level of L_0
$r_{1,i}$ is the one-year rate for experiencing event i at the reduced LDL-C level of L_1
α_i is the rate ratio per unit reduction in LDL-C for event i

As a scenario analysis, the company also explored relationships between LDL-C reductions and CV event risk published by Navarese *et al.* in 2015 and 2018,[48, 49] which were also considered in NICE TA694.[37]

When comparing evinacumab to lomitapide, the results of using Navarese *et al.* showed limited difference to using the CTTC meta-analysis and no change in the decision of cost-effectiveness. [48, 49] The CTTC meta-analysis was therefore preferred in the company's base case, as it was in TA694.[37]

Table 26. Rate ratio for CV events per 1 mmol/L LDL-C reduction. Reproduced from Table 34 in the CS.

CV event	CTTC Meta analysis 2015	TA694 Navarese et al. (2015)	TA694 Navarese et al. (2018)
Stable angina	1	1	1
Unstable angina	0.76 (0.73-0.79)	0.64 (0.43-0.96)	0.85 (0.78-0.96)
MI	0.76 (0.73-0.79)	0.64 (0.43-0.96)	0.85 (0.78-0.96)
TIA	1	1	1
Stroke	0.85 (0.80-0.89)	0.64 (0.43-0.96)	0.99 (0.86-1.08)
CV death	0.88 (0.84-0.91)	0.64 (0.43-0.96)	0.89 (0.73-1.01)

Abbreviations: CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TIA, transient ischaemic attack.

4.2.7.4 EAG critique

The EAG notes that compared to atherosclerotic patients included in the CTTC meta-analysis, HoFH patients are characterised as having a higher risk of experiencing CV events, will experience CV events earlier in life and have higher LDL-C concentrations on and off treatment. As suggested in a retrospective study by Thomspon *et al.*[1] which investigated HoFH patients survival by serum cholesterol, the relationship between on-treatment cholesterol and total mortality may be more exponential rather than linear. As reducing HoFH patient LDL-C may lead to greater reductions in CV event risk compared to those suggested by the CTTC meta-analysis, the company's approach is likely to be conservative. As such, the EAG considers using the CTTC meta-analysis is appropriate.

4.2.7.5 CV event risks and transition probabilities

The company estimated the baseline profile of CV risk events in the model from Thompson *et al.*, to which it then applied the rate reduction of CV events associated with each treatment (as discussed in the previous subsection). In order to do this, and based on NICE appraisals TA385 and TA694,[37, 38] the company utilised the sex and age specific distributions of CV events reported in Ward *et al.* (2007).[42] In the study, fatal and non-fatal CV event data from the Bromley Coronary Heart Disease Register and Oxfordshire Community Stroke Project were used to calculate a ratio of fatal to non-fatal CV events and the proportions of non-fatal CV events (Table 27). The company then applied these ratios to the CVM from Thompson *et al.* to estimate the number of non-fatal CV events, allowing transition probabilities for all CV events to be calculated.

The Company notes that both the Framingham Risk Score (FHS) and QRISK3 algorithm were considered as alternative sources to inform baseline CV event risk but were ultimately rejected due to the underlying differences in the patient populations informing these sources from HoFH patients.

Table 27. Relative rates and proportions of CV events based on Thompson *et al.* and Ward *et al.*[1, 42]

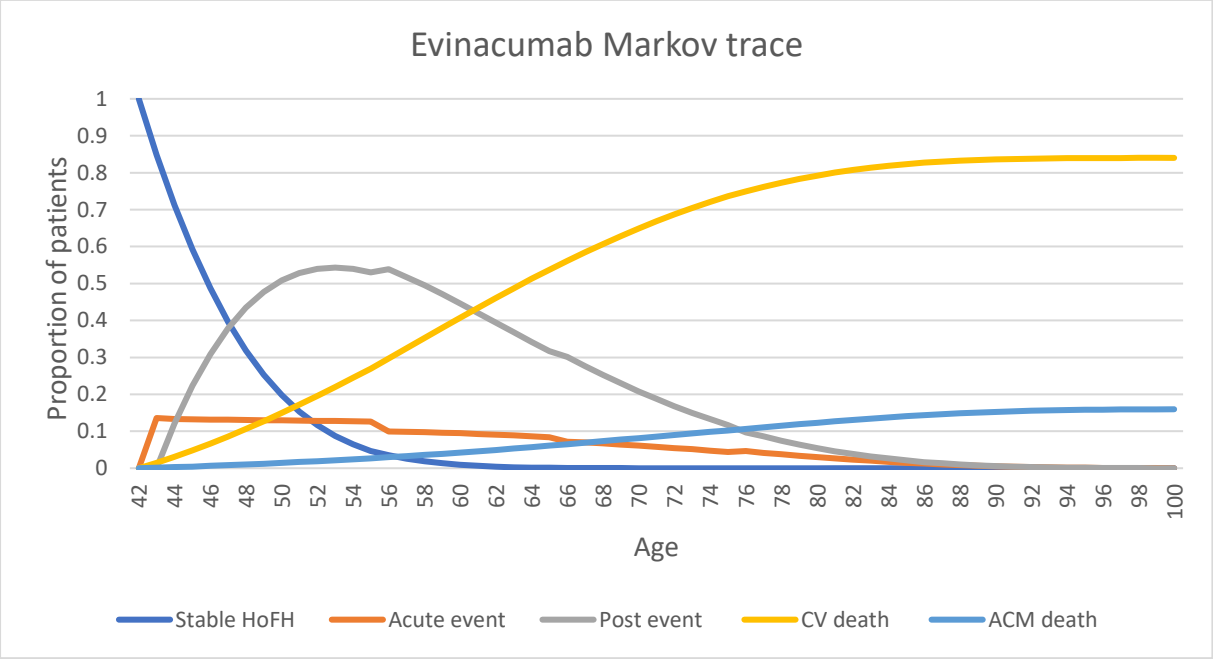
	Age (years)	Stable angina	Unstable angina	MI	TIA	Stroke	CVD death	Non-fatal to fatal CV event ratio
Relative rates of CV events based on Ward *et al.* 2007 (gender adjusted)[42]	40-54*	0.0009	0.0003	0.0006	0.0003	0.0004	0.0003	9.2
	55-65	0.0033	0.0007	0.0014	0.0009	0.0023	0.0012	7.1
	65-74	0.0037	0.0013	0.0027	0.0016	0.0056	0.0029	5.1
	75-84	0.0052	0.0018	0.0041	0.0026	0.0118	0.0044	5.8
	85-100	0.0066	0.0024	0.0054	0.0019	0.0158	0.0053	6.1
Proportions of non-fatal CV events	40-54*	35%	12%	25%	10%	18%	-	-
	55-65	38%	8%	16%	10%	27%	-	-
	65-74	25%	9%	18%	11%	37%	-	-
	75-84	20%	7%	16%	10%	46%	-	-
	85-100	21%	7%	17%	6%	49%	-	-

Abbreviations: CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack.

* An assumption will be made that the CV event distributions for the 45-54 age are applied to younger patient groups.

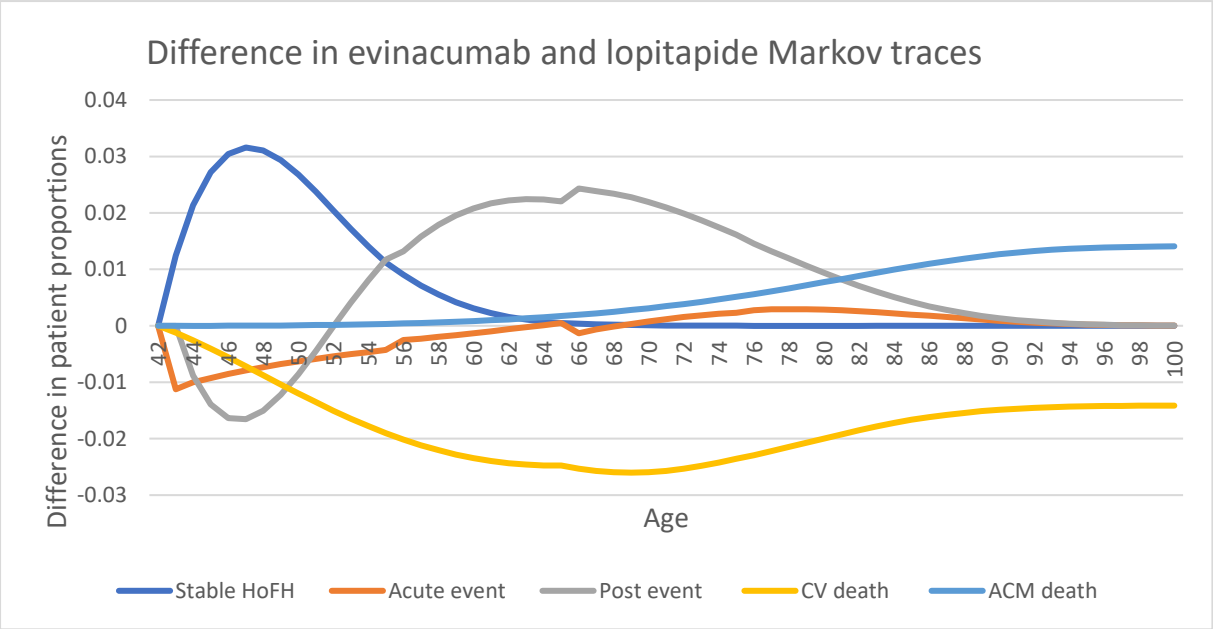
When applying the evinacumab and lomitapide LDL-C reductions, patients travel through the model as described in Figure 12 for evinacumab. As the difference in health state occupancy between the treatments are slight, only the evinacumab Markov trace has been detailed, with Figure 13 displaying the difference between evinacumab and lomitapide Markov traces. The differences in life years between the treatments are shown in Table 28.

Figure 12. Evinacumab Markov Trace.



Abbreviations: ACM, all-cause mortality; CV, cardio-vascular; HoFH, homozygous familial hypercholesterolaemia.

Figure 13. Difference in evinacumab and lomitapide Markov traces.



Abbreviations: ACM, all-cause mortality; CV, cardio-vascular; HoFH, homozygous familial hypercholesterolaemia.

Table 28. Economic model life years by treatment arm.

Health outcomes (LYs)	Evinacumab	Lomitapide	Difference
Stable HoFH	4.18	3.93	0.25
Stable angina	0.25	0.26	-0.01
Unstable angina	0.34	0.36	-0.02
MI	0.68	0.71	-0.03
TIA	0.07	0.07	0
Stroke	0.74	0.76	-0.02
Post-Stable angina	0.96	0.92	0.04
Post-Unstable angina	1.08	1.07	0.01
Post-MI	2.26	2.24	0.02
Post-TIA	0.3	0.28	0.02
Post-Stroke	2.29	2.24	0.05
Total life-years	13.16	12.84	0.32

Abbreviations: HoFH, homozygous familial hypercholesterolaemia; MI, myocardial infarction; TIA, transient ischemic attack.

4.2.7.6 EAG critique

Given that the Ward *et al.*[42] study values are specific to the general population, the EAG is concerned with the generalisability of the ratios and CV risks used to derived transition probabilities due to the differences in LDL-C, risk of CV events and disease onset between general population and HoFH patients.

When the EAG consulted clinical experts on the expected ratio of non-fatal to fatal CV events for HoFH patients compared to the general population values described by Ward *et al.*,[42] there was a lack of consensus. While all agreed that HoFH and general population patients would be different, some considered that with respect to the elevated CVM rates experienced by HoFH patients compared to general population, rates of non-fatal events would not increase as much. Others stated they would expect non-fatal events to have a higher comparative incidence to CV fatal events in HoFH patients compared to general population estimates and so the ratio would be higher. The company was therefore asked to conduct a one-way sensitivity analysis as a scenario to test the

sensitivity of the economic model to this assumption. To estimate upper and lower non-fatal to fatal CV event ratios the company increased and decreased the base-case values from Ward *et al.* by 50% (Table 29). When comparing evinacumab to lomitapide there was limited change with the ICER remaining dominant.

Table 29. Fatal to non-fatal CV event ratio sensitivity analysis

Age group	Non-fatal to fatal events incidence ratio		
	Base-case	Base-case*0.5	Base-case*1.5
40-54	9.2	4.6	13.8
55-65	7.1	3.5	10.6
65-74	5.1	2.5	7.6
75-84	5.8	2.9	8.7
85-100	6.1	3.0	9.1

Similarly, although the EAG's clinical experts were unable to provide estimates for the proportions of non-fatal cardiac events for HoFH patients compared to population estimates outlined by Ward *et al.,* they considered that cardiac related events (SA, UA, MI) would be more frequent than cerebrovascular events (TIA, stroke) in HoFH patients compared to general population CVD patients. The company was therefore requested to conduct a scenario analysis in which the frequency of cardiac related events was increased with respect to cerebrovascular events. To conduct this analysis the company increased the proportions of SA, UA and MI by 20% and down weighted the cerebrovascular events to allow relative frequencies to sum to 100%. The change in ICER was negligible when comparing evinacumab to lomitapide as outlined in Section 6.3.

Crucially, as all CV risk and therefore transition probabilities in the model have been indirectly calculated using CVM from the Thompson *et al.*[1] study, which the EAG considers to be overestimated, all transition probabilities to acute health states may similarly be overestimated, leading to overall lower total QALYs and higher total costs in the model. With respect to the incremental differences between treatments, as CVM and baseline probability of CV events may be overestimated in the model, applying the relative decrease in CV risk associated with each treatment is likely to lead to a greater number of CV events avoided for the more efficacious treatment, and therefore higher incremental QALYs and lower incremental costs. For these reasons the calculation of transition probabilities in the model are considered a key issue.

4.2.8 Risk of recurrent events

After patients transition to the post-event state (i.e., after patients experienced a first acute event in the model), the company accounted for the increased probability of recurrent CV events, as was included in NICE TA694 and TA393,[37, 50] by assuming the increases in relative risk as shown in Table 30. Furthermore, a 1.5 increase in the relative risk of CV death was applied to all post-event health states, independently of the first acute event experienced by patients.

Table 30. Relative risks used to capture the increased probability of multiple CV events. Reproduced from Table 35 in the CS.

Increase in probability of recurrent event (Ward *et al.* 2007)	Relative risk (mean)
Risk ratio in cardiac events due to previous cardiac event (UA, SA, MI)	1.5
Risk ratio in cardiac events (SA, UA, MI) due to cerebrovascular event (Stroke, TIA)	1.2
Risk ratio in cerebrovascular events (Stroke, TIA) due to previous cardiac event (UA, US, MI)	1.2
Risk ratio for cerebrovascular events (TIA, stroke) due to previous cerebrovascular events (TIA, stroke)	1.5
Risk ratio of CV death due to history of prior event	1.5

Abbreviations: CV, cardiovascular; MI, myocardial infarction; SA, stable angina; TIA, transient ischaemic attack; UA, unstable angina.

4.2.8.1 EAG critique

The EAG notes that the relative risks assumed in the model are aligned with those of NICE TA694, which also modelled hypercholesterolaemia.

The EAG's clinical experts noted the predisposition to future events after an initial event is likely to be lifelong, therefore, the EAG notes an inconsistency in the company's model, where, for example, if a patient experienced an MI (therefore being at a 1.5 risk of a subsequent cardiac event and a risk of 1.2. of a subsequent cerebrovascular event), but then suffers a cerebrovascular event, then the relative risk of a possible third cardiac event is 1.2. This poses a reduced risk from the previously elevated relative risk of 1.5.

At clarification the EAG requested that the company conducted a scenario where after a cerebrovascular or cardiac event, the relative risk of future events of the same type were permanently increased for the rest of the patient's life. In response to the request, the company

noted that following any non-fatal CV event the risk of the same event occurring is permanently increased by a factor of 1.5 in the model until the next CV event, thus not addressing the EAG issue. As a scenario analysis to explore the sensitivity of the ICER to the relative risk of future events, the EAG increased the relative risk of all future events from any non-fatal CV event to 1.5, the results of which showed that the impact of this assumption is small in the model.

An opinion also provided by the EAG's clinical experts was that not all non-fatal CV events would lead to the same 1.5 relative increase in CVM as assumed in the model. The company was requested to conduct a scenario where event specific increases in relative risk of CVM were applied in the model for each non-fatal CV event. The company noted that due to the structure of the model, independent mortality multipliers could not be implemented for each non-fatal CV. Instead, separate mortality multipliers could be applied for the overarching cardiac and cerebrovascular event types. In the scenario the company varied the mortality ratios associated with each event type in the combinations outlined in Table 31.

The EAG questions the suitability of the apparent arbitrary values used by the company, which in scenarios B9.1 and B9.3, assume that a patient experiencing either a cardiac (B9.1) or cerebrovascular (B9.3) non-fatal CV event would have no increased risk of CVM. The EAG notes that more accurate standardised mortality ratios could have been used for cardiac and cardiovascular events; however, the company's analysis had limited impact on the model's results as seen in Section 5.2.

Table 31. Mortality multiplier sensitivity analysis scenarios

Scenario	Mortality multiplier	
	Cardiac event	Cerebrovascular event
Base-case	1.5	1.5
Scenario B9.1	1	1.5
Scenario B9.2	2	1.5
Scenario B9.3	1.5	1
Scenario B9.4	1.5	2

4.2.9 Health-related quality of life

4.2.9.1 Health state utility values

In ELIPSE, EQ-5D data were collected but these data were not used in the company's model. The company did not provide any justification in the CS for not exploring the use of EQ-5D data from

ELIPSE to inform the economic model. However, the EAG notes that EQ-5D data were only collected from baseline through to week 24 in ELIPSE, and during the double-blind phase of the trial there were no suspected major adverse cardiovascular events reported. As such, the EAG considers that there would not be robust EQ-5D data available from ELIPSE to populate the health states of the model. However, baseline EQ-5D from ELIPSE would be informative for the model and the EAG requested these data from the company during the clarification stage, but this was not provided. The issue of baseline EQ-5D data from ELIPSE is discussed in Section 4.2.9.2.

The company conducted a HRQoL SLR, but as mentioned in Section 4.1, no relevant utility values were identified that could be used to inform the model. Instead, the company conducted a targeted search to identify utility values based on related disease areas to inform the health states in the model. Based on the targeted search, the company selected health-state utility values (HSUVs) from TA694 to inform the model, presented in Table 32.

Table 32. Health-state utility values and multipliers used in the economic model

Health state	Utility value	Mean age (years)	Source	Age- and sex-adjusted utility multiplier
Stable HoFH	0.891	42	Age- and sex-adjusted utility value based on baseline characteristics from ELIPSE, estimated using model 1 from Ara & Brazier. 2010[36]	N/a
Stable angina	0.615	69	Obtained from TA694, based on utility values from Ara & Brazier. 2010.[36, 37]	0.783
Unstable angina	0.615	69		0.783
MI	0.615	69		0.783
Stroke	0.626	68		0.792
Post-stable angina	0.775	68		0.982
Post-unstable angina	0.775	68		0.982
Post-MI	0.742	65		0.924
Post-stroke	0.668	67		0.840
TIA	0.760	73	Obtained from TA694, based on utility values from Luengo-Fernandez *et al*. 2013.[37, 51]	0.994
Post-TIA	0.760	73		0.994

Abbreviations: MI, myocardial infarction; N/a, not applicable; TIA, transient ischaemic attack.

The original source of the HSUVs (except for TIA) in TA694 was a study by Ara and Brazier,[36] which estimated mean EQ-5D utility values for different CV events based on an analysis of general

population data from the 2003 and 2006 Health Survey for England (HSE). The study also presented regression models to estimate baseline utility values, adjusted for age and sex, for the general population (model 1) and for people with no history of CVD (model 2).[36] Ara and Brazier presented a multiplicative approach to estimating HSUVs for comorbid health conditions, which assumes a constant proportional decrement relative to a baseline utility.[36] Utility multipliers for each CV event are estimated by dividing the HSUV for an event by the age-adjusted baseline utility (either general population, which includes people with a history of CVD, or no history of CVD). The authors also presented methods to estimate multipliers for multiple CV events.

Utility values for TIA were not available from Ara and Brazier. Instead, in TA694 the utility value for TIA was from a study by Luengo-Fernandez *et al*. 2013 and was assumed to be the same for the post-TIA utility.[51]

Based on the methods in Ara and Brazier and in line with the recommendations in NICE DSU TSD 12, the company adopted the multiplicative approach to estimate HSUVs for the model.[36, 52] The company's approach is also consistent with in TA393, TA394 and TA694.[37, 50, 52, 53]

For the economic model, the company used regression model 1 (presented below) from Ara and Brazier,[36] to calculate a general population baseline utility value to estimate the utility value multiplier for each CV event (presented in Table 32). The proportion of males from ELIPSE (46% male) was used to inform the regression.

$$EQ-5D = 0.950857 + 0.212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

As an example, the multiplier for MI (0.783) was calculated by dividing the HSUV for MI (0.615) by the estimated general population utility value for a 68.8-year-old (0.786).

Background age-and sex-adjusted general population utility values were estimated for each model cycle, using a starting age of 42 years and baseline proportion of males (46%) from ELIPSE and updates annually as the cohort ages over the model time horizon. Background utility is also used to inform the stable HoFH health state. The utility multipliers were then applied to the background utility values per cycle to capture the impact of CV events for each health state.

4.2.9.2 EAG critique of health state utility values

Generally, the approach the company has taken to estimate HSUVs for the model is consistent with NICE DSU TSD 12 and previous related TAs.[37, 50, 52] The EAG would like to see the baseline utility from ELIPSE, as this would more accurately reflect the underlying health condition and thus enable a comparison of the age- and sex-adjusted baseline utility for the stable HoFH health state at the start of the model. However, the EAG considers that as there are no treatment-specific adjustments to HSUVs, any changes to baseline utilities would affect both arms of the model equally.

In TA694, for the MI and post-TIA health states, the EAG preferred to use different utility values, which were accepted by the submitting company during technical engagement. However, for the current analysis, the company used the submitting company's original base case utility values for those health states. For the MI utility, it was originally assumed that the utility value would be the same as stable angina and the post-MI utility value was based on the post-heart attack utility from Ara and Brazier.[36] However, in the Ara and Brazier study, an acute heart attack utility (0.721) was available and the EAG in TA694 preferred this for their base case. Additionally, in the Luengo-Fernandez *et al*. 2013 study, which was the source of the TIA utility, an estimate for 12 months (0.78) was available which could be used to inform the post-TIA health state and this were accepted in TA694.[37] Thus, for consistency, the EAG has included the TA694 preferred utility values for MI and post-TIA to inform the utility multipliers in its preferred base case, presented in Section 6.4.

A fundamental issue that runs through the entire cost-effectiveness analysis is the issue of the population included in the model and how the model structure reflects this. As discussed in Sections 4.2.3 and 4.2.4, the company modelled a primary prevention population (no history of CV events) and no distinction is made in the model, in terms of costs and QALYs, between first and subsequent CV events. In other words, the model doesn't capture a patient's CV event history and thus does not capture the costs and QALY impact of worsening health.

The EAG considers that a model structure that does distinguish between first and subsequent CV events, as well as multiple CV events, in an attempt to capture CV history, would be more appropriate for the decision problem and would allow proper estimation of costs and utilities. Furthermore, utility values are available in the Ara and Brazier study that distinguish for people with no history of CVD, first events, history of CVD and multiple events which could be implemented if the model structure more accurately reflected the disease pathway for HoFH patients.

During the clarification stage, the company supplied a scenario which distributed the initial cohort amongst the stable HoFH and post-event health states to capture both primary and secondary prevention patients. The scenario had limited impact on the ICER. However, the EAG considers that the scenario has limitations as utility values for the secondary prevention patients having acute events and then moving to a post-event health state is the same as for primary prevention patients experiencing their first event and moving to a post-event health state. Table 33 presents a comparison of the utility values for patients with a history of CV disease and utility values used in the model, based on data from Ara and Brazier (2010).[36] As shown in the table, the drop in patients' utility, both for the acute event period and the post-acute event, from baseline would be higher if the company had more appropriately captured the change in patients' utility as suggested by the EAG.

Table 33. Secondary prevention health state multiplier values – Ara and Brazier 2010[36]

Health state	Used in the model – scenario analysis for secondary prevention patients			Secondary prevention as suggested by the EAG at clarification		
	Baseline utilities in the model	Acute CV event (event < 12 months, history of just event)	Post CV event (no event < 12 months, history of event)	Baseline utilities	Acute CV event (event <12 months, history of event + other cv condition)	Post CV event (no event <12 months, history of event + other cv condition)
Angina	0.775	0.615	0.775	0.775	0.541	0.715
Unstable angina	0.775	0.615	0.775	0.775	0.541	0.715
MI	0.742	0.615	0.742	0.742	0.431	0.685
Stroke	0.668	0.626	0.668	0.668	0.479	0.641

Abbreviations: CV, cardiovascular; MI, myocardial infarction.

4.2.9.3 Disutility associated with LDL-apheresis

LDL-apheresis is an intensive treatment, akin to dialysis, and is provided weekly or fortnightly. Typically, patients on LDL-apheresis will require frequent vascular access, but more permanent vascular access options, such as a fistula, may be required as apheresis is generally used as a long-term treatment option. As such, the company assumed a disutility for patients receiving LDL-apheresis. The company was unable to identify a disutility value associated with LDL-apheresis in published literature and instead used a disutility value associated with haemodialysis as a proxy.

The company identified a study by Beaudet *et al*. 2014 which was a review of utility values for economic modelling in Type 2 diabetes.[54] In the study, a disutility of -0.164 for haemodialysis was estimated based on a utility value of 0.621 for patients on haemodialysis, sourced from a paper by Wasserfellen *et al*. 2004, subtracted from a utility value for Type 2 diabetes patients without complications (0.785).[54, 55] The company considered that in the UK, on average, haemodialysis is given three times per week for four hours. In contrast, the company assumed LDL-apheresis is given once every two weeks for 2.5 hours on average.

The company assumed that the disutility per hour between haemodialysis and LDL-apheresis is equivalent. As such, the company estimated the disutility per hour associated with haemodialysis treatment as 0.0034, which is based on a month of treatment (48 hours). The company then estimated that the number of hours of LDL-apheresis treatment per month was five hours (two treatments per month with a duration of 2.5 hours) and multiplied this by the haemodialysis disutility per hour to estimate an LDL-apheresis disutility of 0.0171. In the submission, the company state this is an annual disutility, but based on the calculation, the EAG considers that the LDL-apheresis disutility is for a month of treatment.

4.2.9.4 EAG critique

The EAG considers including a disutility for LDL-apheresis is appropriate, especially as the EAG's clinical experts advised that it is an intensive treatment and one that would negatively impact a patient's quality of life. The EAG's clinical experts considered that assuming the HRQoL impact of LDL-apheresis was akin to haemodialysis was not unreasonable. However, as mentioned in Section 4.2.9.3 the company's disutility estimate reflects a monthly disutility rather than an annual estimate, as described in the CS. As such, the EAG ran a scenario adjusting the monthly LDL-apheresis disutility to an annual estimate (-0.205) and this is presented in Section 6.3 and included in the EAG's preferred assumptions presented in Section 6.4.

As evinacumab is an IV treatment, the EAG explored whether it was reasonable to include a disutility associated with treatment with its clinical experts. The EAG's clinical experts considered that IV treatment would have a negligible impact on HRQoL and that the treatment frequency of evinacumab (once monthly) compared to other treatments (daily oral treatments or weekly/ fortnightly apheresis) would be seen by patients to be a benefit. Therefore, the EAG considers that it is reasonable for a disutility associated with IV treatment to be excluded from the model.

4.2.10 Resource use and costs

The company included the following costs in the economic model: drug acquisition, administration, monitoring, health state and adverse events. The details for each of these are given in the following subsections.

Unit costs used in the model reflect 2021/22 prices and where necessary, published costs for previous years were inflated using the ONS consumer price index (CPI) inflation indices for 2022.[56]

A confidential patient access scheme (PAS) discount is available for evolocumab and lomitapide. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

4.2.10.1 Drug acquisition costs

The intervention considered for the economic analysis is evinacumab as an adjunct to diet and other LDL-C lowering therapies (background treatments).

Evinacumab is a variable dose drug that is dosed based on body weight at 15 mg per kilogram (kg), it's administered as an intravenous (IV) infusion over 60 minutes, once monthly. The list price of evinacumab is [redacted] per 345 mg vial. A simple PAS discount of [redacted] on the list price of evinacumab is available, resulting in a discounted price of [redacted] per 345 mg vial. For the base case, the company assumed vial wastage, which the EAG's clinical experts considered a reasonable assumption.

In ELIPSE, mean weight was estimated to be 72.7 kg. However, to account for vial wastage, the company considered that it was appropriate to estimate a distribution of patient weight associated with different vial combinations to calculate a weighted average number of vials per administration.

To estimate the number of evinacumab vials per treatment administration, the company calculated weight thresholds associated with different combinations of vials. The company then estimated the proportion of patients that would require each combination of vials based on the weight threshold by assuming a lognormal distribution of weight, using the mean weight from ELIPSE (72.7 kg). Table 34 presents the number of evinacumab vials and the proportion of patients assumed for each weight category.

The weighted average number of vials per administration was estimated to be 3.7 vials. The annual cost of evinacumab in the base case was estimated to [redacted]. If mean weight from ELIPSE was used directly to estimate mean number of vials per administration, this would result in 3.2 vials per administration, resulting in an annual cost of [redacted] (company scenario for vial sharing).

Table 34. Evinacumab vial combinations (reproduced from Table 41 of the CS)

Number of evinacumab vials (345 mg)	Weight threshold (kg)*	Proportion of patients (based on lognormal distribution)
6 vials	138	3.6%
5 vials	115	12.5%
4 vials	92	35.9%
3 vials	69	41.5%
2 vials	46	6.5%
1 vial	23	0.0%

Abbreviations: Kg, kilogram; mg, milligram.

*Weight threshold based on dose of 15 mg/ kg and a vial size of 345 mg. For example, 345 mg / 15 mg = 23 kg weight threshold for a single vial.

Background LLTs considered in the model are presented in Table 35 and are applied equally to both the evinacumab and lomitapide arms of the model. The proportion of patients that receive each background treatment is described in Table 23. Drug costs and dose for HoFH patients were obtained from the British National Formulary (BNF).[57]

Table 35. Background lipid-lowering treatment costs

Background lipid-lowering treatment	Treatment regimen	Pack size	Cost per pack	Annual cost	Source
Atorvastatin	80 mg once daily	28 x 80 mg tablets	£1.40	£10.83	NICE BNF 2022[57]
Evolocumab	420 mg once monthly. For patients on apheresis, 420 mg once every two weeks	2 x 140 mg per 1 ml pre-filled disposable injections	£340.20	£8,909.71*	NICE BNF 2022[57]
Ezetimibe	10 mg once daily	28 x 10 mg tablets	£1.53	£13.18	NICE BNF 2022[57]
LDL apheresis	IV infusion once every 2 weeks	N/A	£1,526.25	£39,818.94	Thompson *et al*. 2008[58]

Abbreviations: BNF, British National Formulary; mg, milligram; ml, millilitre; N/A, not applicable

*Cost is weighted by the proportion of patient on apheresis who will receive evolocumab once every two weeks,

The company considered that the main comparator for the base case is lomitapide. The EAG considers that lomitapide is not the only appropriate comparator and this issue is discussed fully in Section 4.2.2.

In the lomitapide SmPC, it is recommended that the starting dose is 5 mg once daily. After 2 weeks the dose may be increased, according to LDL-C response and based on acceptable safety and tolerability, to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and to the maximum recommended dose of 60 mg.[59] It should be noted that lomitapide is available in 5 mg, 10 mg and 20 mg capsules and the cost is the same for all strengths (£17,765 per 28 capsule pack).

The company used dose data from the lomitapide pivotal trial[16] to estimate the weighted average number of capsules per day to include in the model. In the lomitapide trial, out of 23 patients who completed the study, the maximal dose was 5 mg in one subject; 20 mg in five subjects; 40 mg in six subjects and 60 mg in 11 subjects.[16] Based on this data, presented in Table 36, the company estimated a weighted average of 2.22 lomitapide capsules per day to include in the model. The annual cost of lomitapide was calculated to be £513,854.

Table 36. Lomitapide dose from Cuchel *et al*. 2013[16]

Number of capsules	Dose	Number of patients (n=23)	Proportion
1 capsule	5mg or 20 mg	6	26.1%
2 capsules	40 mg	6	26.1%
3 capsules	60 mg	11	47.8%

Abbreviations: mg, milligram.

4.2.10.2 EAG critique of drug acquisition costs

Drug acquisition costs are a primary driver of cost-effectiveness in the model and constitute approximately 99% of costs for both evinacumab and lomitapide arms of the model. The EAG considers that the company's estimation of number of vials per administration is thorough but resulted in an estimate which was not whole vials (3.7 vials). The EAG considers that the calculation of vials per administration should have been rounded up to the nearest vial (four vials). The EAG ran a scenario exploring four vials per administration and results are presented in Section 6.3 and this has been included in the EAG's preferred assumptions, presented in Section 6.4.

With regards to the treatment regimen for LDL apheresis, the EAG's clinical experts advised that LDL apheresis can be given weekly. As such, during the clarification stage the EAG requested, and the company provided, a scenario exploring a weekly treatment regimen for LDL-apheresis and these results are presented in Section 5.2.2. The EAG notes that in ELIPSE, LDL-apheresis was allowed weekly or once every two weeks. However, the EAG considers that company has taken a conservative approach to the cost of LDL-apheresis, by assuming a once every two week regimen and this can be considered reasonable.

In the base case, the company assumed that 32.3% of patients had a null/null mutation based on data from ELIPSE. For patients with a null/null mutation, treatments including PCSK9 inhibitors, atorvastatin and ezetimibe are ineffective. In the model, the proportion of patients on PCSK9 inhibitors (76.9%), statins (93.8%) and ezetimibe (75.4%) are derived from ELIPSE and thus accounts for treatments given to patients with the null/null mutations. However, the EAG's clinical experts advised that statins and ezetimibe wouldn't be given to patients with a null/null mutation. Therefore, the EAG considers that the proportions, and thus the costs, of atorvastatin and ezetimibe may not be reflective of UK clinical practice for patients with a null/null mutation. However, in the EAG's preferred assumptions for the comparison with LLTs, treatment efficacy is derived from ELIPSE and therefore using the LLT treatment mix from the trial maintains the link between efficacy and costs. Nonetheless, atorvastatin and ezetimibe are relatively inexpensive treatments and so the EAG considers that if costs of these treatments were reduced to reflect UK clinical practice for patients with a null/null mutation, this would have a limited impact on the ICER.

In the scenario comparing evinacumab to the continuation of LLTs, the proportion of patients costed on treatments was in line with ELIPSE, as described in Section 2.3.1. Similar to the comparison against lomitapide, the difference in drug costs between evinacumab and LLTS was almost entirely responsible for all of the incremental costs. The results of the scenario are outlined in Section 6.3.

4.2.10.3 Drug administration costs

The company assumed no administration costs for oral drugs and evolocumab, which is a self-administered injection.

For evinacumab, the company assumed administration of the IV infusion would require one hour of Band 5 nurse time, at a cost of £46 per administration, sourced from PSSRU 2022.[60] The annual cost of administration for evinacumab in the model was £552.

4.2.10.4 EAG critique of drug administration costs

Generally, the company's approach to administration costs is reasonable. A minor issue raised by the EAG's clinical experts was that the first administration of an IV drug requires longer nurse time than subsequent administrations. The EAG's clinical experts considered that two to three hours of nurse time would be required for the first administration of evinacumab. As such, during the clarification stage the EAG requested, and the company provided, a scenario exploring 2.5 hours of nurse time for the first administration of evinacumab followed by 1 hour of nurse time for all subsequent administrations.

The resulting annual evinacumab administration cost for the scenario was £621 for the first year and £552 for all subsequent years. The EAG notes that the company's scenario in response to clarification B34 assumed the annual administration cost was £621 for both first and subsequent years, which is incorrect but can be considered a bias against evinacumab. The company's scenario had a negligible impact on the cost-effectiveness results. However, the EAG ran a corrected administration cost scenario, presented in Section 6.3 and included the this in the EAG preferred base case presented in Section 6.4.

4.2.10.5 Treatment discontinuation

In ELIPSE, no patients discontinued treatment with evinacumab because of AEs. [redacted]. As such, the company assumed no treatment discontinuation for patients on evinacumab. Additionally, the company did not assume treatment discontinuation for atorvastatin, ezetimibe or evolocumab.

As mentioned in Section 4.2.7, lomitapide is associated with known hepatoxicity and so patients who are not able to tolerate treatment are identified early on in treatment. In the pivotal study for lomitapide, four out of 29 patients (13.79%) discontinued treatment due to adverse events.[16] As such, the company assumed that within 26 weeks of treatment, 13.79% of patients would discontinue treatment with lomitapide. After 26 weeks, the company assumed there would be no further treatment discontinuations for patients on lomitapide, due to a lack of longer-term data. The EAG's clinical experts considered that not many patients discontinue treatment with lomitapide and that a one-off treatment discontinuation was not unreasonable, as patients who can tolerate treatment are unlikely discontinue treatment in the longer term.

The company assumed a one-off treatment discontinuation for patients on LDL-apheresis for both arms of the model based on data from the pivotal trial of lomitapide. In the lomitapide trial, 18 patients were on LDL-apheresis at baseline and three of those patients permanently discontinued treatment during the study. For the model, the company assumed the one-off treatment discontinuation rate was 10.34% (three patients out of 29 patients in the ITT population). However, the EAG notes that the denominator in the company's LDL-apheresis treatment discontinuation calculation includes all patients in the study and not just patients on LDL-apheresis. This is discussed further in Section 4.2.10.6.

4.2.10.6 EAG critique of treatment discontinuation

The EAG considers that the estimation of the LDL apheresis discontinuation rate should be estimated using only data on patients on LDL apheresis (i.e. the denominator in the discontinuation calculation should be the total number of patients on LDL-apheresis) in Cuchel *et al*.[16] As such, the EAG estimates that the LDL-apheresis discontinuation rate should be 16.67%. The EAG ran a scenario using its preferred estimate for the LDL-apheresis discontinuation rate and results are presented in Section 6.3 and it is also included in the EAG preferred assumptions, presented in Section 6.4.

4.2.10.7 Monitoring costs

The company were unable to identify monitoring costs related specifically to HoFH. Instead, the company based assumptions of monitoring costs for patients on treatment based on guidance in NICE CG181, which has been used in related NICE guidance (TA385, TA393,TA394 and TA694).[37, 38, 50, 53] As mentioned in Section 4.2.7, additional liver monitoring tests are recommended for patients initiating treatment with lomitapide to prevent liver-related AEs.[59] In its updated base case post-clarification, the company assumed three liver monitoring tests and a Fibroscan® test annually for lomitapide patients (outlined in response to clarification question B36). The monitoring assumptions and costs applied in the economic model are presented in Table 37.

Table 37. Monitoring resource use and costs

Resource use	Unit cost	Evinacumab		Lomitapide		Source
		First year	Subsequent years	First year	Subsequent years	
Routine appointments						
Blood sample appointment	£9.04	2	1	2	1	NICE CG181 for resource use and unit cost.[61] Source of unit cost from CG181 was

						PSSRU (2013), which has been inflated to 2022 prices in the model.
GP appointment	£64.36	2	2	2	2	NICE CG181 for resource use and unit cost.[61] Source of unit cost from CG181 was PSSRU (2013), which has been inflated to 2022 prices in the model. However, the unit cost from CG181 was £45, but a cost of £46 has been used in the model. See Section 6.1 for EAG's correction to the model.
Blood test						
Total cholesterol	£1.40	2	1	2	1	NICE CG181 for resource use and NHS reference costs 2013/14, sourced from TA385, for unit costs.[38, 61] Additional monitoring resource used assumed for lomitapide patients based on guidance in SmPC.[61]
HDL cholesterol	£1.40	2	1	2	1	
Liver function tests (ALT or AST)	£1.40	2	1	5*	4	
Fibroscan®	£88.00	N/a	N/a	1	1	Additional monitoring resource used assumed for lomitapide patients based on guidance in SmPC.[59] Unit cost based on NHS reference costs 2021/22 (HRG code RD48Z).[62]
Total annual monitoring costs	**-**	**£155.20**	**£141.97**	**£247.40**	**£234.16**	**-**

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GP, general practitioner; HDL, high-density lipoprotein; n/a, not applicable.

*In response to clarification B36, the company explained that additional liver function test for subsequent years (3) was assumed for the first year for lomitapide patients.

4.2.10.8 EAG critique of monitoring costs

The EAG identified a correction needed for the estimation of the costs associated with blood sample and GP appointment. For the model, the company used the cost of an appointment to take a blood sample and the cost of a GP appointment from CG181 directly and inflated these to 2022 prices. However, in CG181 these costs were obtained from PSSRU 2013.[61] Additionally, the cost of a GP appointment in CG181 was £45, but the company used a cost of £46. However, the EAG considers that based on the CS, the company meant only to use the resource use estimates from CG181 and use costs from the latest PSSRU guidance. As such, the EAG has corrected the costs and presents a corrected company base case in Section 6.1.

The EAG disagrees with the company's use of costs from CG181 for blood tests, which were originally sourced from NHS reference costs for 2013/14. Instead, blood test costs should be sourced from the latest NHS reference costs (2021/22) using the cost code for phlebotomy services (DAPS08).[62] During the clarification stage, the EAG requested, and the company provided a scenario, using the cost code for phlebotomy services (DAPS08) from NHS reference costs 2021/22 (£4.70) to inform the cost of blood tests in the model, but did not change their base case. The EAG considers that the company's base case cost for blood tests is inappropriate and instead includes the latest NHS reference cost for phlebotomy services (DAPS08) to inform the cost of blood tests in its preferred assumptions, presented in Section 6.4.

With regards to the resource use assumed for monitoring costs, the EAG's clinical experts agreed that there would be increased liver monitoring for patients on lomitapide but advised that other assumptions included in the model are not reflective of UK clinical practice and instead proposed alternative assumptions, presented in Table 38. Additionally, the lomitapide SmPC recommends that liver related tests are performed at least monthly in the first year and then at least every three months in subsequent years.[59] The EAG ran a scenario using the assumptions presented in Table 38 and results are presented in Section 6.3 and these have also being included in the EAG's preferred assumptions in Section 6.4.

Table 38. EAG's preferred monitoring costs based on clinical expert monitoring resource use assumptions and including SmPC monitoring recommendations for lomitapide

Resource use	Unit cost	Evinacumab		Lomitapide		Source
		First year	Subsequent years	First year	Subsequent years	
Routine appointments						

Blood sample appointment	£11.10	3	2	3	2	PSSRU 2022.[60] Based on cost of Band 4 community-based scientific and professional staff. Appointment time of 18 minutes assumed based on CG181.[61]
GP appointment	£42.00	2	2	2	2	PSSRU.[60] Cost of GP appointment.
Specialist appointment	£113.00	4	2	4	2	PSSRU 2022.[60] Cost per working hour of a hospital based consultant doctor.
Blood test						
Total cholesterol	£4.70	3	2	3	2	NHS reference costs 2021/22 (HRG code DAPS08).[62]
HDL cholesterol	£4.70	3	2	3	2	
HbA1c	£4.70	1	1	1	10	
Liver function tests (ALT or AST)	£4.70	3	2	12	4	
Fibroscan®	£88.00	N/a	N/a	1	1	Additional monitoring resource used assumed for lomitapide patients based on guidance in SmPC.[59] Unit cost based on NHS reference costs 2021/22 (HRG code RD48Z).[62]
Total annual monitoring costs	**-**	**£654.85**	**£405.71**	**£785.15**	**£503.11**	**-**

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GP, general practitioner; HDL, high-density lipoprotein; n/a, not applicable.

4.2.10.9 Health state costs

As with monitoring costs, the company was unable to identify health state costs related to HoFH from the resource use and costs SLR. Instead, the company performed a targeted literature search was conducted to identify health state costs used in previous cost-effectiveness models in CVD. Based on the targeted search, the company selected health state costs reported in TA694 to inform the model.[37] Table 40 summarises the health state costs included in the model and descriptions of the costs are presented thereafter.

Table 39. Health state costs used in the economic model (reproduced from Table B41 of the company's clarification response)

Health state	Unit cost (TA694)	Inflated cost (2022 prices)	Source and assumptions
Stable HoFH	-	£9,760	Assumed to be the same as stable angina
Stable angina	£7,907	£9,760	Cost taken directly from TA694 based on cost of first six months after an event from CG181, inflated to 2018 prices.[37, 61]
Post-stable angina	£245	£303	Cost taken directly from TA694 based on annual cost from CG181, inflated to 2018 prices.[37, 61]
Unstable angina	£2,469	£3,048	Cost taken directly from TA694 based on incremental mean cost for Months 1-6 plus half incremental annualised mean cost for Months 7-36 for first and second events combined from Danese *et al*. 2016, inflated to 2018 prices.[37, 63]
Post-unstable angina	£381	£471	Cost taken directly from TA694 based on incremental annualised mean cost for Months 7-36 for first and second events combined from Danese *et al*. 2016, inflated to 2018 prices.[37, 63]
MI	£4,862	£6,001	Cost taken directly from TA694 based on incremental mean cost for Months 1-6 plus half incremental annualised mean cost for Months 7-36 for first and second events combined from Danese *et al*. 2016, inflated to 2018 prices.[37, 63]
Post-MI	£980	£1,210	Cost taken directly from TA694 based on incremental annualised mean cost for Months 7-36 for first and second events combined from Danese *et al*. 2016, inflated to 2018 prices.[37, 63]
Stroke	£8,618	£12,254	TA393.[50] Annual cost
Post-stroke	£1,769	£2,515	TA393.[50] Annual cost
TIA	£2,011	£2,483	Cost taken directly from TA694 based on incremental mean cost for Months 1-6 plus half incremental annualised mean cost for Months 7-36 for first and second events combined from Danese *et al*. 2016, inflated to 2018 prices.[37, 63]
Post-TIA	£810	£1,000	Cost taken directly from TA694 based on incremental annualised mean cost for Months 7-36 for first and second events combined from Danese *et al*. 2016, inflated to 2018 prices.[37, 63]
CV death	-£236	-£291	Cost taken directly from TA694 based on the difference between the cost of a CV and non-CV death from Walker *et al*. 2016, inflated to 2018 prices.[37, 64]

Abbreviations: CV, cardiovascular; HoFH, homozygous familial hypercholesterolaemia; MI, myocardial infarction; TIA, transient ischaemic attack

For the stable angina acute and post-event health states, costs from TA694 were sourced from CG181.[61] In CG181, the acute event cost is for the first six months after an event and the post-event costs are annual. However, the EAG is unclear if the company adjusted the acute event health state costs from CG181 to reflect an annual cost and this issue is discussed further in Section 4.2.10.97.

In TA694, the primary source of health state costs for unstable angina, MI and TIA was from a study by Danese *et al*. 2016, which was a retrospective cohort study of patients treated with lipid-modifying therapy.[63] The study assessed Clinical Practice Research Datalink (CPRD) records from 2006 to 2012 to identify individuals with their first and second CV-related hospitalisations and estimated mean total and incremental costs related to first and second CV events.[63] Additionally, mean costs were estimated for the first six months after an event and for months 7-36 (annualised) thereafter.[63] For the estimates of incremental costs, the authors used the costs estimated for the 12 month period before the first CV event as the baseline for both first and second event incremental costs.[63] The study reported costs separately for first and second events, as well as combined first and second event costs.

For the base case, the company used the first and second event combined incremental costs from Danese *et al*. 2016 to inform the model for the unstable angina, MI and TIA acute and post event health states. For the acute event health states in the model, the company used the Months 1-6 costs plus half of the annualised mean costs associated with Months 7-36 from the study to estimate an annual cost. For the post-event health states, the annualised mean costs for Months 7-36 were used. Use of incremental costs instead of total costs and the adjustment to the acute event cost to be annual was accepted by the EAG in TA694 as appropriate and can be considered reasonable for the current analysis.

In TA694, the EAG preferred to use stroke costs (acute and post-event) presented in the EAG critique for TA393 as part of the preferred base case as these were deemed to be reflective of UK clinical practice. In the EAG report for TA393, the EAG sourced acute stroke costs from a UK population-based study by Luengo-Fernandez *et al*. 2006 and post-stroke event costs another UK based study by Youman *et al*. 2003.[65, 66] In their clarification response to question B41d, the company updated their base case to use the EAG's preferred costs from TA393.

In TA694, the cost of CV death was obtained from Walker *et al*. 2016, which was a study using UK registry data to estimate healthcare use and costs in patients with stable coronary artery disease.[64]

In the study, the cost of CV and non-CV death was estimated (£2,008 and £2,240, respectively) and the company for TA694 used this data to estimate an incremental cost saving of CV death. For the current appraisal, the company adopted the same approach used by the company in TA694 to estimate a cost saving for CV death.

4.2.10.10 EAG critique of health state costs

The EAG has several issues with the company's approach to the estimation of health state costs included in the model and considers that all health state costs required amendment.

The EAG is concerned with how health state costs from TA694 were inflated to 2022 prices used to inform the model. The company took the 2018 inflated health state costs presented in the company submission for TA694, which were inflated using the PSSRU hospital & community health services index and inflated them to 2022 prices using the latest ONS CPI inflation indices. As such, two different inflation indices have been used to estimate the health state costs included in the model. Furthermore, the EAG was unable to verify the company's final health state costs in the model (which were hardcoded) based on the unit costs presented in Table B41 of the company clarification response and using the ONS CPI inflation index to inflate these to 2022 prices.

Instead, the EAG considers that the company should have obtained the health state unit costs directly from the primary sources presented in the EAG report for TA694 and inflated these using ONS CPI inflation index. As such, the EAG obtained unit costs and price years from all the primary sources described in TA694 and inflated these to 2022 prices using the ONS CPI inflation index, presented in Table 40. The EAG's preferred health state costs were explored in a scenario, presented in Section 6.3 and included in its preferred assumptions, presented in Section 6.4.

Table 40. EAG preferred health state costs

Health state	Source cost	Cost year	Inflated cost (2022 prices)	Source and assumptions
Stable HoFH	-	-	£10,992.30	Assumed to be the same as stable angina.
Stable angina	£7,856.00	2014	£10,992.30	CG181.[61] Acute cost of £7,736 was a 6-month cost. Annual cost for the model estimated as the acute cost plus half the annual post-stable angina event cost.
Post-stable angina	£240.00	2014	£335.81	CG181.[61]
Unstable angina	£2,416.00	2014	£3,380.52	Danese *et al.*2016. Incremental mean cost for Months 1-6 (£2,229.42) plus half incremental annualised mean cost for

				Months 7-36 for first and second events combined.[63]
Post-unstable angina	£373.15	2014	£522.12	Danese *et al*.2016.[63] Incremental annualised mean cost for Months 7-36 for first and second events combined.
MI	£4,756.62	2014	£6,655.57	Danese *et al*.2016.[63] Incremental mean cost for Months 1-6 (£4,277.23) plus half incremental annualised mean cost for Months 7-36 for first and second events combined.
Post-MI	£958.78	2014	£1,341.55	Danese *et al*.2016.[63] Incremental annualised mean cost for Months 7-36 for first and second events combined.
Stroke	£6,906.00	2005	£12,819.33	TA393 based on Luengo-Fernandez *et al*. 2006.[50, 65]
Post-stroke	£1,257.00	2002	£2,537.24	TA393 based on Youman *et al*. 2003.[50, 66]
TIA	£1,967.98	2014	£2,753.64	Danese *et al*.2016.[63] Incremental mean cost for Months 1-6 (£1,571.55) plus half incremental annualised mean cost for Months 7-36 for first and second events combined.
Post-TIA	£792.85	2014	£1,109.37	Danese *et al*.2016.[63] Incremental annualised mean cost for Months 7-36 for first and second events combined
CV death	£1,174	2014	£1,642.69	CG181.[61]

Abbreviations: CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack

Using unit costs directly from the primary sources presented in the EAG report for TA694 overcomes a particular issue with acute and post-event stable angina costs. The company directly took the inflated costs for acute and post-event stable angina costs from the company submission for TA694. However, the EAG for TA694 considered that the unit costs for acute and post-event stable angina (which were based on CG181) were incorrectly inflated. As such, the EAG corrected the acute and post-event stable angina costs this was accepted by the submitting company as part of technical engagement.[37]

Furthermore, in CG181 the acute cost for stable angina was a 6-month cost. The EAG is unclear if the cost taken from TA694 was adjusted to be an annual cost. However, as the EAG prefers to use costs directly from the primary source, the acute stable angina cost was adjusted to annual cost by employing the same methodology the company just for the acute costs from Danese *et al*. 2016, which was to use the 6-month cost plus half the annual post-event event cost. The adjusted acute

stable angina cost was then inflated from 2014 prices to 2022 prices using only the ONS CPI inflation index. The adjusted cost for Stable angina is presented in Table 40.

With regards to the cost of CV death, the EAG was concerned that the company adopted the same approach as the submitting company for TA694, which was to estimate a cost saving of CV death (compared to non-CV death). In TA694, the EAG preferred to use the cost of CV death from CG181 and this was accepted by the submitting company as part of technical engagement. Therefore, the EAG considers the same approach to the cost of CV death should be adopted for the current analysis and had used the CV death cost from CG181 as part of its preferred health state costs, presented in Table 40.

A fundamental issue that runs through the entire cost-effectiveness analysis is the issue of the population included in the model and how the model structure reflects this. As discussed in Section 4.2.4, the company modelled a primary prevention population (no history of CV events) and did not make a distinction, in terms of costs and QALYs, between primary and subsequent CV events appropriately. The scenario analysis provided by the company, which aimed to include a secondary prevention population in the model did not distinguish costs for first and second events separately. However, as noted in EAG report for TA694, first and second event costs from Danese *et al*., 2016 are generally consistent and so in terms of estimating total costs for the model, it is unlikely to make a substantial difference.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 41 presents the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) gain of [redacted] over lomitapide along with cost savings of [redacted] for evinacumab, generates a dominant incremental cost-effectiveness ratio (ICER). Using the £20,000 and £30,000 threshold, the net health benefit (NHB) is [redacted] and [redacted] QALYs.

A proposed confidential patient access scheme (PAS) discount for evinacumab is applied in the company's base case and is therefore reflected in the results presented in this report. A confidential PAS discount is available for evolocumab and lomitapide. As such, the External Assessment Group (EAG) has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

Table 41. Company's updated base case results (post-clarification)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Lomitapide	5,976,577	12.84	10.05	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Lomitapide	6,029,571	12.96	10.12	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

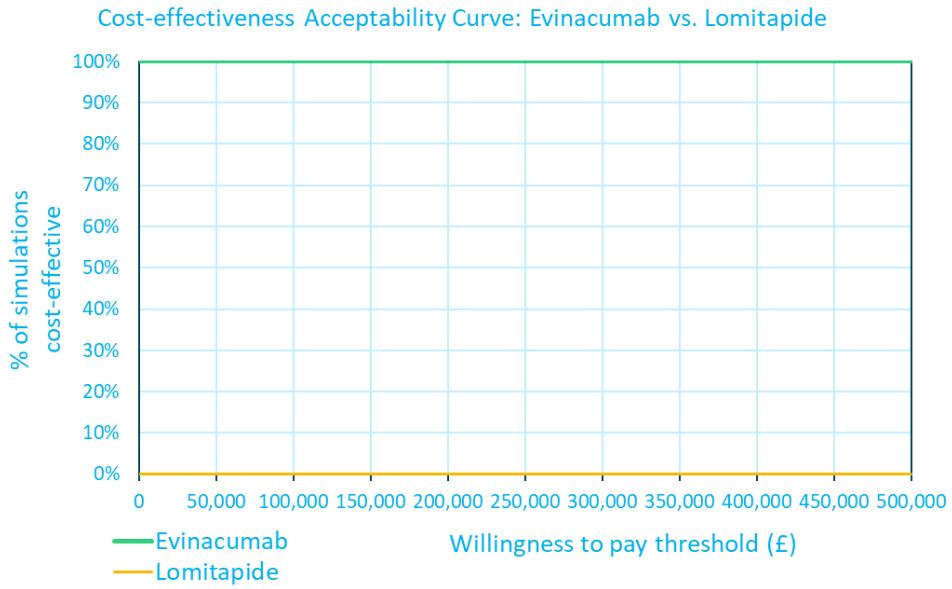
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

A PSA scatterplot is presented in Figure 14 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 15. Based on these analyses, the probability that evinacumab is cost effective versus lomitapide is 100% at a willingness to pay (WTP) threshold of £20,000 and £30,000.

The EAG considers the parameters and respective distributions chosen for PSA to be generally sound (see Table 46 of the company submission [CS] for PSA inputs). The EAG also considers the probabilistic results to be comparable to the deterministic results.

Figure 14. PSA scatterplot – evinacumab versus lomitapide (reproduced from Figure 1 of the company clarification response)

Figure 15. Cost-effectiveness acceptability curve – evinacumab vs. lomitapide (reproduced from Figure 2 of the company clarification response)



5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact, on the ICER, of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated using the tornado diagram in Figure 16. The ICER was most sensitive to baseline age, parameters for the Gompertz distribution to model baseline risk and short lomitapide discontinuation rate.

Figure 16. Tornado plot – evinacumab versus lomitapide (reproduced from Figure 30 in the CS).

5.2.2 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. Details of each scenario are provided in Table 52 of the company submission. In addition, the company conducted several additional scenario analyses requested by the EAG. Results of all the scenario analyses conducted by the company are presented in Table 42.

Table 42. Company scenario analyses – evinacumab versus lomitapide (reproduced from Table 6 of the company clarification response)

ID	Scenario	Incremental costs (£)	Incremental QALYs	ICER
-	Base case	[redacted]	[redacted]	Dominant
1	Apheresis efficacy LDL-C reduction 50.4% (Pottle *et al.* (2019))	[redacted]	[redacted]	Dominant
2	Patient lower mean body weight of 60kg	[redacted]	[redacted]	Dominant
3	Assume for evinacumab no unused vial wastage	[redacted]	[redacted]	Dominant
4	Evinacumab given on 4-weekly rather than monthly basis	[redacted]	[redacted]	Dominant
5	Evinacumab underdosed up to 20% based on target weight	[redacted]	[redacted]	Dominant
6	Choice of survival function: Log-logistic distribution	[redacted]	[redacted]	Dominant
7	Alternative utility source: TA395	[redacted]	[redacted]	Dominant
8	Alternative cost source: TA395	[redacted]	[redacted]	Dominant
9	Evinacumab discontinuation 50% of lomitapide	[redacted]	[redacted]	Dominant
10	Link between 1 mmol/L LDL-C change and CV rate reduction alternative source (Navarese *et al.* (2015))	[redacted]	[redacted]	Dominant
11	Link between 1 mmol/L LDL-C change and CV rate reduction alternative source (Navarese *et al.* (2018))	[redacted]	[redacted]	Dominant
12	Assuming 1.5% discount rate for costs and utilities	[redacted]	[redacted]	Dominant
13	Evinacumab efficacy 50.9% (ELIPSE RCT vs placebo with lomitapide patients removed)	[redacted]	[redacted]	Dominant
EAG requested scenarios				
14	EAG Scenario B1.1 (Distributing patients across health states at baseline)	[redacted]	[redacted]	Dominant
15	EAG Scenario B1.1 + B9.1	[redacted]	[redacted]	Dominant
16	EAG Scenario B1.1 + B9.2	[redacted]	[redacted]	Dominant
17	EAG Scenario B1.1 + B9.3	[redacted]	[redacted]	Dominant
18	EAG Scenario B1.1 + B9.4	[redacted]	[redacted]	Dominant
19	EAG Scenario B6.1 (Lower non-fatal to fatal incidence event ratio)	[redacted]	[redacted]	Dominant
20	EAG Scenario B6.2 (Higher non-fatal to fatal incidence event ratio)	[redacted]	[redacted]	Dominant
21	EAG Scenario B7.1 (20% higher proportion of cardiac events in all CV events)	[redacted]	[redacted]	Dominant

22	EAG Scenario B9.1 (Lower relative risk of CV mortality for cardiac events)	[redacted]	[redacted]	Dominant
23	EAG Scenario B9.2 (Higher relative risk of CV mortality for cardiac events)	[redacted]	[redacted]	Dominant
24	EAG Scenario B9.3 (Lower relative of CV mortality for cerebrovascular events)	[redacted]	[redacted]	Dominant
25	EAG Scenario B9.4 (Higher relative risk of CV mortality for cerebrovascular events)	[redacted]	[redacted]	Dominant
26	EAG Scenario B13.1 (Cost minimisation analysis of evinacumab versus lomitapide)	[redacted]	[redacted]	Dominant
27	EAG Scenario B19.1 (Removing age adjustment multipliers from health state utility values)	[redacted]	[redacted]	Dominant
28	EAG Scenario B20.1 (Alternative utility value of 0.721 for MI)	[redacted]	[redacted]	Dominant
29	EAG Scenario B22.1 (Using HSE 2014 general population utility values)	[redacted]	[redacted]	Dominant
30	EAG Scenario B24.1 (Assuming zero disutility associated with apheresis)	[redacted]	[redacted]	Dominant
31	EAG Scenario B28.1 (Assuming 75% patients on background apheresis treatment)	[redacted]	[redacted]	Dominant
32	EAG Scenario B31.1 (Assuming apheresis is given weekly)	[redacted]	[redacted]	Dominant
33	EAG Scenario B34.1 (Assuming the first IV administration last for 2.5 hours for evinacumab)	[redacted]	[redacted]	Dominant
34	EAG Scenario B37.1 (Alternative source for cost of blood tests)	[redacted]	[redacted]	Dominant
35	EAG Scenario B40.1 (More frequent monitoring appointments and tests)	[redacted]	[redacted]	Dominant

Abbreviations: CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life year; RCT, randomised controlled trial.

5.3 Model validation and face validity check

Quality assurance of the model using a structured quality check procedure, composed of black and white box testing as well as internal and face validity checks of the model, was performed by the

company's principal developer and a senior economic modeller not involved in the model development.

The company also performed an external validation of the survival function for time to CV death by replicating survival functions for time to CV death for patients on lomitapide presented in a study by Leipold *et al*. 2017.[67]

The EAG identified a correction needed for the estimation of costs for a blood sample appointment and a GP appointment and this is described further in Section 6.1.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

NICE provided the External Assessment Group (EAG) with prices for atorvastatin and ezetimibe from the Drugs and pharmaceutical electronic market information tool (eMIT) to be used in the economic model. Based on eMIT, the price of 28-tablet pack of atorvastatin 80 mg was £0.83 and for 28-tablet pack of ezetimibe 10 mg was £1.01.[68] The EAG has updated the model with the eMIT prices as part of the corrections to the company base case.

As described in Section 4.2.10.8, the EAG considers that based on the CS, the company meant only to use the resource use estimates from CG181 and use costs from the latest PSSRU guidance to estimate costs of a blood sample appointment and a GP appointment (rather than take the costs from CG181 as well). In CG181, the cost of a blood sample appointment was based on the cost of a clinical support worker in PSSRU 2013.[39] One hour of clinical support worker time was estimated as £21 and the cost of a blood sample appointment based on this is CG181 was £6.46. As such the EAG estimates that the assumed time of a blood sample appointment was approximately 18 minutes. In the latest PSSRU guidance, clinical support workers are included under the category of community-based scientific and professional staff and the cost per working hour of a Band 4 staff member was £37.[39] Thus the cost for an 18 minute appointment was estimated to be £11.10. The cost of a GP appointment in PSSRU 2022 was estimated to be £42.

Both costs have been corrected by the EAG with the corrected company base case outlined below (Table 43).

Table 43. Company's corrected base case post-clarification.

#	Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
0	Post-clarification company base case							
	Lomitapide	5,976,576	12.84	10.05	-	-	-	-
	Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
1	EAG corrected company base case							
	Lomitapide	5,975,874	12.84	10.05	-	-	-	-
	Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year.

6.2 Exploratory and sensitivity analyses undertaken by the EAG.

In Section 4 of this report, the EAG has described several scenarios that warranted further exploration in addition to the company's own sensitivity and scenario analyses. The EAG cost effectiveness and cost minimisation scenarios comparing evinacumab to lomitapide are listed below, with results presented in Section 6.3. The results of the cost effectiveness scenarios comparing evinacumab to LLTs (lipid lowering therapies) are presented in Table 43 of Section 6.3. All net health benefit (NHB) calculations assumed a willingness to pay threshold of £30,000.

In the confidential appendix, scenarios with patient access scheme (PAS) discounts for lomitapide and evolocumab have been applied.

- Assuming 30% of patients are primary prevention patients and 70% are secondary prevention patients – 4.2.3
- Using the baseline LDL-C from ELIPSE and removing background treatment effects - 4.2.7.1
- Using the treatment efficacies from the MAIC with lomitapide patients removed from the evinacumab treatment arm- 4.2.7.1
- Relative risk of recurrent CV events increased from 1.5 to 2 - 4.2.8
- TA694 preferred utility values for MI (0.721) and post-TIA (0.78) to inform the utility - multipliers for those health states - 4.2.9.1
- Annual LDL-apheresis disutility of -0.205 - 4.2.9.3
- Four vials per evinacumab administration - 4.2.10.3
- Evinacumab administration cost scenario (£621 for the first year, £552 for subsequent years) - 4.2.10.3
- LDL-apheresis discontinuation rate of 16.67% - 4.2.10.5
- EAG's preferred monitoring costs based on clinical expert monitoring resource use assumptions and including SmPC monitoring recommendations for lomitapide - 4.2.10.7
- EAG preferred health state costs – 4.2.10.9
- Cost minimisation of evinacumab against lomitapide using the ELIPSE base line LDL-C - 4.2.7.1
- Cost effectiveness analysis of evinacumab against continuation of LLTs using baseline LDL-C and treatment efficacies from ELIPSE - 4.2.2

6.3 EAG scenario analysis

In the scenarios conducted by the EAG, evinacumab remained the more cost-effective treatment when compared to lomitapide, with the ICER remaining dominant. However, the EAG notes that in scenario 2 which used the baseline LDL-C from ELIPSE and MAIC treatment effects when lomitapide treated patients are excluded from the evinacumab arm the, ICER lies in the south-west quadrant of the cost-effectiveness plane as evinacumab is less efficacious and less costly compared to lomitapide.

In the scenarios comparing evinacumab to the continuation of LLTs, evinacumab led to additional costs and QALYs with all ICERS being between £2.5 to £3M/QALY.

Table 44. Results of the EAG's scenario analyses comparing evinacumab to lomitapide

#	Results per patient	Evinacumab (1)	Lomitapide (2)	Incremental value (1-2)
0	Company base case (corrected)			
	Total costs (£)	[redacted]	£5,975,874	[redacted]
	QALYs	[redacted]	10.05	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]
1	Assuming 30% of patients are primary prevention patients and 70% are secondary prevention patients			
	Total costs (£)	[redacted]	£5,868,122	[redacted]
	QALYs	[redacted]	9.70	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]
2	Using ELIPSE baseline LDL-C and removing background treatment effects			
	Total costs (£)	[redacted]	£5,782,668	[redacted]
	QALYs	[redacted]	9.70	[redacted]
	ICER (£/QALY)			Dominant
	iNHB			[redacted]
3	Using the MAIC treatment efficacies when excluding lomitapide treated evinacumab patients			
	Total costs (£)	[redacted]	£5,975,874	[redacted]
	QALYs	[redacted]	10.05	[redacted]
	ICER (£/QALY)			£24,322,725 (SW)
	iNHB			[redacted]
4	Relative risk of recurrent CV events increased from 1.5 to 2			
	Total costs (£)	[redacted]	£5,571,374	[redacted]
	QALYs	[redacted]	9.39	[redacted]
	ICER (£/QALY)	-	-	Dominant

	iNHB	-	-	[redacted]
5	TA694 preferred utility values for MI (0.721) and post-TIA (0.78) to inform the utility - multipliers for those health states			
	Total costs (£)	[redacted]	£5,975,874	[redacted]
	QALYs	[redacted]	10.13	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]
6	Annual LDL-apheresis disutility of -0.205			
	Total costs (£)	[redacted]	£5,975,874	[redacted]
	QALYs	[redacted]	9.26	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]
7	Four vials per evinacumab administration			
	Total costs (£)	[redacted]	£5,975,874	[redacted]
	QALYs	[redacted]	10.05	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]
8	Evinacumab administration cost scenario (£621 for the first year, £552 for subsequent years)			
	Total costs (£)	[redacted]	£5,975,874	[redacted]
	QALYs	[redacted]	10.05	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]
9	LDL-apheresis discontinuation rate of 16.67%			
	Total costs (£)	[redacted]	£5,972,242	[redacted]
	QALYs	[redacted]	10.05	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]
10	EAG's preferred monitoring costs based on clinical expert monitoring resource use assumptions and including SmPC monitoring recommendations for lomitapide			
	Total costs (£)	[redacted]	£5,979,466	[redacted]
	QALYs	[redacted]	10.05	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]
11	EAG preferred health state costs			
	Total costs (£)	[redacted]	£5,996,896	[redacted]
	QALYs	[redacted]	10.05	[redacted]
	ICER (£/QALY)	-	-	Dominant
	iNHB	-	-	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; iNHB, incremental net health benefit; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; QALY, quality adjusted life year; SmPC,

summary of product characteristics; SW, south-west quadrant ICER; TA, technology assessment; TIA, transient ischemic attack.

Table 45. Evinacumab and lomitapide cost-minimisation analysis using baseline LDL-C from ELIPSE

Outcomes	Technology		Cost difference (£)
	Evinacumab (£)	Lomitapide (£)	
Cost results assuming equal efficacy			
Drug costs	[redacted]	5,867,368	[redacted]
Monitoring costs	1,262	1,262	0
Health state costs	14,244	14,244	0
CV death costs	-2,984	-2,984	0
Total costs	[redacted]	5,882,874	[redacted]

Abbreviations: CV, cardiovascular; SoC, standard of care.

Table 46. Results of the EAG's scenario analyses comparing evinacumab to continuation of LLTs.

#	Results per patient	Evinacumab (1)	SoC LLTs (2)	Incremental value (1-2)
0	Baseline LDL-C and treatment efficacies from ELIPSE			
	Total costs (£)	[redacted]	£241,585	[redacted]
	QALYs	[redacted]	8.83	[redacted]
	ICER (£/QALY)	-	-	£2,678,877
	iNHB	-	-	[redacted]
1	Assuming 30% of patients are primary prevention patients and 70% are secondary prevention patients			
	Total costs (£)	[redacted]	£236,356	[redacted]
	QALYs	[redacted]	8.55	[redacted]
	ICER (£/QALY)	-	-	£2,780,907
	iNHB	-	-	[redacted]
2	Relative risk of recurrent CV events increased from 1.5 to 2			
	Total costs (£)	[redacted]	£224,420	[redacted]
	QALYs	[redacted]	8.19	[redacted]
	ICER (£/QALY)	-	-	£2,554,085
	iNHB	-	-	[redacted]
3	TA694 preferred utility values for MI (0.721) and post-TIA (0.78) to inform the utility - multipliers for those health states			
	Total costs (£)	[redacted]	£241,585	[redacted]
	QALYs	[redacted]	8.93	[redacted]
	ICER (£/QALY)	-	-	£2,716,205
	iNHB	-	-	[redacted]
4	Annual LDL-apheresis disutility of -0.205			

	Total costs (£)	[redacted]	£241,585	[redacted]
	QALYs	[redacted]	8.13	[redacted]
	ICER (£/QALY)	-	-	£2,893,336
	iNHB	-	-	[redacted]
5	Four vials per evinacumab administration			
	Total costs (£)	[redacted]	£241,585	[redacted]
	QALYs	[redacted]	8.83	[redacted]
	ICER (£/QALY)	-	-	£2,930,602
	iNHB	-	-	[redacted]
6	Evinacumab administration cost scenario (£621 for the first year, £552 for subsequent years)			
	Total costs (£)	[redacted]	£241,585	[redacted]
	QALYs	[redacted]	8.83	[redacted]
	ICER (£/QALY)	-	-	£2,678,910
	iNHB	-	-	[redacted]
7	LDL-apheresis discontinuation rate of 16.67%			
	Total costs (£)	[redacted]	£238,378	[redacted]
	QALYs	[redacted]	8.83	[redacted]
	ICER (£/QALY)	-	-	£2,678,129
	iNHB	-	-	[redacted]
8	EAG's preferred monitoring costs based on clinical expert monitoring resource use assumptions and including SmPC monitoring recommendations for lomitapide			
	Total costs (£)	[redacted]	£245,685	[redacted]
	QALYs	[redacted]	8.83	[redacted]
	ICER (£/QALY)	-	-	£2,678,237
	iNHB	-	-	[redacted]
9	EAG preferred health state costs			
	Total costs (£)	[redacted]	£266,074	[redacted]
	QALYs	[redacted]	8.83	[redacted]
	ICER (£/QALY)	-	-	£2,676,051
	iNHB	-	-	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; iNHB, incremental net health benefit: LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; QALY, quality adjusted life year; SmPC, summary of product characteristics; SW, south-west quadrant ICER; TA, technology assessment; TIA, transient ischemic attack.

6.4 EAG preferred assumptions

Listed below are the EAG's preferred base case assumptions. Table 47 outlines the cumulative impact of the assumptions listed below.

- Assuming 30% of patients are primary prevention patients and 70% are secondary prevention patients;
- Using the baseline LDL-C from ELIPSE and removing background treatment effects;
- TA694 preferred utility values for MI (0.721) and post-TIA (0.78) to inform the utility multipliers for those health states;
- Annual LDL-apheresis disutility of -0.205;
- Four vials per evinacumab administration;
- Evinacumab administration cost scenario (£621 for the first year, £552 for subsequent years);
- LDL-apheresis discontinuation rate of 16.67%;
- EAG's preferred monitoring costs based on clinical expert monitoring resource use assumptions and including SmPC monitoring recommendations for lomitapide;
- EAG preferred health state costs.

As the EAG considers the MAIC excluding the patients on lomitapide in the evinacumab arm of ELIPSE to be more consistent with the company's positioning of evinacumab in the treatment pathway and the continuation of LLTS to be a comparator of interest, the EAG has applied the cumulative impact of the EAG-preferred assumptions to two EAG bases cases.

The first EAG base case is a cost effectiveness analysis between evinacumab and lomitapide which uses the MAIC treatment effects when excluding lomitapide patients from the evinacumab arm (Table 48). The second is a cost effectiveness analysis comparing evinacumab to the continuation of LLTs using the treatment effects from ELIPSE (Table 49).

The EAG endeavoured to conduct a PSA to assess the sensitivity of the ICERs to parameters' uncertainty. However, this was not possible due to errors in the PSA in the company's model sent in their clarification response on the 14th of July 2023. The only possibility to run the PSA was using a previous version of the model, but the EAG was not able to adjust the model parameters to reflect updated to the model as the PSA and DSA code reset all parameters to the default (base case) values.

Additionally, the EAG notes that the deterministic and probabilistic results were consistent using the previous model, however it appears that the confidence intervals for the MAIC results have been inputted incorrectly, with positive values at the extreme ends being used for negative values (for

example, 28.73 not -28.73, as per the results reported in Section 3.4.4). As such the EAG recommends at TE that the company updates the model to remove the restrictions tying parameters to their default values for all sensitivity analyses and corrects the MAIC confidence interval errors in the model.

The EAG additionally assessed the model against the scenarios conducted by the company when assuming the alternative MAIC treatment effects and continuation of LLTs as a comparator. The ICER's under both modelling assumptions were robust against each scenario with no change in the nature of the ICER.

Table 47. EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER (£/QALY)
Company corrected base case (post clarification)	-	Dominant
Assuming 30% of patients are primary prevention patients and 70% are secondary prevention patients	4.2.3	Dominant
Using the baseline LDL-C from ELIPSE and removing background treatment effects	4.2.7.1	Dominant
TA694 preferred utility values for MI (0721) and post-TIA (0.78) to inform the utility multipliers for those health states	4.2.9.1	Dominant
Annual LDL-apheresis disutility of -0.205	4.2.9.3	Dominant
Four vials per evinacumab administration	4.2.10.3	Dominant
Evinacumab administration cost scenario (£621 for the first year, £552 for subsequent years).	4.2.10.3	Dominant
LDL-apheresis discontinuation rate of 16.67%	4.2.10.5	Dominant
EAG's preferred monitoring costs based on clinical expert monitoring resource use assumptions and including SmPC monitoring recommendations for lomitapide	4.2.10.7	Dominant
EAG preferred health state costs	4.2.10.9	Dominant

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; QALY, quality adjusted life year; SmPC, summary of product characteristics; TA, technology assessment; TIA, transient ischemic attack.

Table 48. EAG base case 1 – Evinacumab and lomitapide cost effectiveness analysis using the MAIC treatment effects with lomitapide treated patients excluded in evinacumab arm & EAG assumptions

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Lomitapide	5,700,073	12.20	8.73	-	-	-	-

Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,193,589 (SW)
Abbreviations: ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality adjusted life year; SW, south-west quadrant ICER.							

Table 49. EAG base case 2 – Evinacumab and SoC LLTs cost effectiveness analysis using ELIPSE treatment effects & EAG assumptions

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
LLTs	262,092	11.16	7.98	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,336,965
Abbreviations: ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality adjusted life year.							

6.5 Conclusions of the cost effectiveness sections.

Overall, the EAG notes that the key parameters driving the cost-effectiveness results are the sources used for the relative treatment effects for lomitapide vs evinacumab, the inclusion of background LLT as a comparator to evinacumab in the model and the treatment acquisition costs.

Additionally, the EAG considers that the *de novo* model developed by the company is overly simplistic. The model lacks the ability to distinguish and therefore account for the difference in health outcomes of patients' experiencing primary or subsequent CV events. Given the majority of patients in ELIPSE would be considered secondary prevention patients and that the EAG's clinical experts considered that the secondary prevention population may be closer to 70% at 42 years of age, this is a critical issue with the model which the EAG considers should be addressed at technical engagement (TE).

The EAG is also concerned with the company's use of the Thompson *et al.* study which has been used to inform CV risk, baseline LDL-C and transition probabilities in the model. [1] While the available literature describing CV risk in HoFH patients is limited and therefore the use of Thompson *et al.* can be accepted to a certain extent given no appropriate alternative, the EAG considers that the company's approach to adjusting baseline LDL-C from Thompson *et al.* to reflect the background LLTs from ELIPSE introduces unnecessary uncertainty and lacks methodological robustness. The EAG considers that using the baseline LDL-C from ELIPSE would have been more appropriate and provide

robust results as it already accounts for a more representative mix of background LLTs used in the UK.

As the EAG considers that the MAIC excluding the patients on lomitapide in the evinacumab arm of ELIPSE to be more consistent with the company's positioning of evinacumab in the treatment pathway and that LLTs are an additional comparator of interest, the EAG has provided two base cases.

When comparing evinacumab to lomitapide the EAG found evinacumab to be less efficacious but also less costly, resulting in an ICER of £25,193,589, positioned in the south-west quadrant of the cost effectiveness plane. Lastly, when comparing evinacumab to LLTs, evinacumab led to additional costs and QALYs with the resulting ICER being £3,336,965.

Overall, the EAG recommends that at technical engagement (TE) the company conducts the following updates to the model:

1. Updates the model to account for costs and utility differences between primary and secondary events as described by Danese *et al.* and Ara and Brazier.[36, 63]
2. Updates the economic model so that the PSA is functional when different input parameters are used in the model and the resetting of values to default removed.
3. Corrects the use of the credible intervals from the MAIC in the PSA.

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Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG 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 14 August** 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 EAG's preferred estimate of relative efficacy of evinacumab in reducing LDL-C

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG has estimated the efficacy of evinacumab in the model using data from the MAIC from the ELIPSE cohort with patient receiving lomitapide removed. This is a fundamental change which results in evinacumab as reducing LDL-C by -33.83% (-96.84 to 29.17%) compared with baseline, which is not statistically significant, and is less effective than lomitapide -40.1% (-51.47 to 28.73%). This is relevant to several sections, including: Section 1.3 (page 16) Section 3.4.4 (page 63)	There are several ways the efficacy of evinacumab could be estimated which should be discussed during the technical engagement. The following are a selection of estimates we believe much more closely represent the true effectiveness of evinacumab: • -49.0% (95% CI -65.00 to -65.0 to -33.1%). Naïve data compared with placebo, ELIPSE (n=65). • -47.1% (95% CI -65.00 to -65.0 to -33.1%). Naïve data compared with baseline, ELIPSE (n=43). • -50.9 (95% CI -58.8 to -42.0). Cohort with lomitapide patients removed compared with placebo, ELIPSE (n=51). • -46.4% (distributional data not currently available). Cohort with lomitapide patients removed compared with baseline.	In several places in the EAG report, they assert their use of the MAIC estimate is used because it is "more consistent with the company's positioning of evinacumab in the treatment pathway". Whilst this may be superficially true, this MAIC value was not used because the estimated sample size (ESS) was 3.9. We believe it is a factual truth (not opinion) that this value is statistically unstable and therefore cannot reliably be used to inform the efficacy of evinacumab. Using this value should also be rejected because: • It discards nearly all the valuable data generated by ELIPSE, a high quality RCT assessed at low risk of bias which recruited 65 patients with no discontinuations (exceptionally rare in the field of HoFH and in contrast to lomitapide, which had a smaller single-armed study as its pivotal trial) • The point estimate of -33.8% is lower than any other value that	Not a factual inaccuracy, no change required.

Section 3.5 (page 64) Section 4.2.7.2 (page 84) Section 6.4 (page 126) Section 6.5 (page 128)	• -55.08 (95% CI –71.90 to 38.27%). Full MAIC as intended a priori (ESS=9.9) Note in all these cases, this empirical data is statistically significantly superior to placebo or baseline, which is consistent with all the current studies on evinacumab. These values are dependent on the assumption that the efficacy of evinacumab (and indeed lomitapide) are independent of age, baseline LDL-C and, crucially, concomitant drug treatment, which is consistent with the assumptions made in the model.	could be derived from the MAIC (with all other estimates showing numerical superiority of evinacumab over lomitapide), and much lower than actually observed in ELIPSE or any of the other studies • Because the ESS is 3.9, the confidence intervals are extremely wide and this constitutes a non-significant result, again contrary to all the other results data available (R1500-CL-1331 and R1500-1719). • The EAG notes results from "R1500-CL-1719 [are likely] to be highly uncertain" (n=14 study, page 65 of report), yet advocates the use of an n<4 study, which does not seem logical. Using this efficacy for evinacumab means it is associated with lower QALY gains compared with lomitapide and to the SW quadrant of the ICER plane, which we believe does not represent reality in any way. We therefore ask that this value is reconsidered to better represent the true efficacy of evinacumab. **Major impact.**	

Issue 2 Company has not considered adolescent population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG "notes that there is no assessment of the cost-effectiveness of evinacumab in adolescents presented in the CS and that the company does not provide a rationale for why this population has not been considered separately" Section 2.1 (page 22)	Request to remove this statement.	The company have given a rationale for the omission of this CE scenario in Section B.1.1 of the submission where is stated "there are only very limited comparative evidence in this subgroup which is insufficient to allow for robust cost effectiveness analysis". This is further expanded in Section B.2.7.4. Additionally many other aspects of the model reflect ELIPSE, which as has been pointed out by the EAG, only recruited 2 patients in this age range and had an average age of 42 years; thus the model is not designed to reflect this age group. **Minimal impact.**	The EAG thanks the company for highlighting this and has deleted the text "*and that the company does not provide a rationale for why this population has not been considered separately*".

Issue 3 Mutations associated with HoFH

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG states "Patients with HoFH have functional mutations in genes that impair the low-density	Request to reword sentence.	Not all mutations relate to LDLR; other pathways, such APOB and PCSK9 are also relevant (although affect fewer people).	The EAG thanks the company for highlighting this and has amended the text in the EAG report to "*Patients with HoFH have functional mutations in genes*

lipoprotein receptor (LDLR) pathway". Section 2.2 (page 22)		**Correction, minimal impact**	*such as low-density lipoprotein receptor (LDLR), apolipoprotein B (ApoB), proprotein convertase subtilisin/kexin type 9 (PCSK9)*"

Issue 4 Position of evinacumab (and lomitapide) in EAS 2023 consensus guidelines.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"LDL apheresis appears to be considered at the same line as lomitapide (and/or evinacumab)" Section 2.2.1 (page 24)	We believe this is a misinterpretation of EAS 2023. Request to amend as appropriate.	Lomitapide and/or evinacumab are used with or without LDL apheresis in these recommendations, meaning the pharmacological options are used first with LDL apheresis to be used as a possible adjunct. That is, LDL apheresis would not be used instead of these drugs or as a replacement for them, meaning it is used as the next line of therapy (note: lines of therapy are not explicit in EAS 2023). **Minor impact (as EAS 2023 not used in CEM).**	The EAG thanks the company for highlighting this and has removed the sentence from the EAG report.

Issue 5 Size of population eligible for evinacumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The EAG is therefore concerned with the company's positioning of evinacumab as a replacement for lomitapide as this could be a much larger population than those currently receiving lomitapide" Section 2.3.3. (page 37)	Request to remove word "much"	We believe the adjective "much" in this context is hyperbolic and implies the eligible population would be an order of magnitude more, when in fact the context is more a handful of people, in the UK. **No impact, but misleading.**	The EAG thanks the company for highlighting this and has updated the text in the EAG report to remove the word '*much*' from Section 1.3 and Section 2.3.3.

Issue 6 Impact of background LLT on lomitapide [or evinacumab]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The EAG notes that in the discussion section of the study publication for Cuchel et al. it is reported that the percentage reduction in LDL-C was "similar to that	Request to provide correct reference. Provide acknowledgement in the report there is no grounded concerns for believing lomitapide or evinacumab interact with other LLTs	Factual clarification, the publication in question (included in the pack) is: "Stefanutti C, Blom DJ, Averna MR, et al. The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia - a post-hoc	Not a factual inaccuracy, no change required. The reference in the EAG report is correct and the text in the EAG report includes the following: "*and this therefore suggests lomitapide*

observed during lomitapide monotherapy in HoFH patients" from another publication" Section 3.4.1 (page 61) Section 3.5 (page 66)	in such a way as to affect their efficacy.	analysis of a Phase 3, single-arm, open-label trial. *Atherosclerosis.* 2015;240(2):408-414". On a general note, in several places the EAG conveys concern that other forms of LLT may impact on the efficacy of lomitapide or evinacumab in terms of relative LDL-C reduction. In actual fact, there is no rationale we are aware of to suggest this is the case and there is empirical evidence, for instance the study by Stefanutti and the extensive subgroup analysis performed in ELIPSE, that this is not the case. Both have mechanisms of action that are independent of all other forms of LLT, and no synergy or antagonism is anticipated. All evidence suggests their effect is additive. **Potentially large implications for efficacy estimates**	*has similar efficacy when added to existing background LLTs.*"

Issue 7 Longer-term extension studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"However, the EAG is unclear why analysis at a later timepoint was not also	Request to remove sentence or add company rationale.	The reasons for this were explained in Section B.2.9.3.6 of the company submission. Whilst patient attrition was not an issue for ELIPSE, it was a	The EAG thanks the company for highlighting this and has updated the text in the EAG report to "*In addition, the EAG notes that both*

considered by the company given that both studies had long-term extension studies” Section 3.4.2 (page 62)		serious issue for Cuchel et al. pivotal study on lomitapide, where patient attrition exceeded 20%, meaning it was not possible to interpret the long term results for this study. **Minimal impact**	*studies had long-term extension studies but the company considered attrition to be a serious issue for Cuchel et al. (the lomitapide study), as patient attrition exceeded 20%, and therefore did not consider it appropriate to use these data*.”

Issue 8 Limited sample size of studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“The EAG considers the results from the MAICs to be uncertain, and potentially confounded due to the small sample size (in both studies)” Section 3.4.4 (page 63)	Request to correct inaccuracy.	Technical accuracy. The limited sample size is not a confounder, it is a fundamental limitation of the studies available, particularly regarding lomitapide, which cannot be controlled for. **Minimal impact**	The EAG thanks the company for highlighting this and has updated the text in the EAG report and removed the text “*potentially confounded due to the small sample size*”. The EAG has also updated the related text in Section 1.3 and Section 3.4.4.

Issue 9 Incorrect sample size stated for R1500-CL-1719

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The EAG notes that there are data for [redacted] patients from the interim analysis of the long-term, single-arm Study R1500-CL-1719, but also notes that these are non-comparative data." Section 3.5 (page 65)	Request to correct quoted sample size to n=14	The sample size quoted is incorrect, as 14 adolescents were investigated (12 new and 2 previously included in ELIPSE). **Minimal impact**	The EAG thanks the company for highlighting this and has updated the EAG report to "[redacted] *patients*".

Issue 10 Incorrect reporting of NHB values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Using the £20,000 and £30,000 threshold, the net health benefit (NHB) is [redacted] and [redacted]" Section 6.1 (page 119)	To update [redacted] and [redacted]" to "[redacted] and [redacted] QALYs"	For accuracy in reporting **Minimal impact**	The EAG thanks the company for highlighting this and has updated the units of measurement for the NHB in the EAG report.

Issue 11 Inconsistent reporting in scenario analysis table

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 44, scenario #1, row 3 for the ICER (£/QALY) value, 'Dominant' should be stated rather than the negative ICER, for consistency, and to avoid potential confusion Section 6.3 (page 122)	To update to 'Dominant'	For consistency in reporting **Minimal impact**	The EAG thanks the company for highlighting this and has updated the ICER for this scenario to "*dominant*" in the EAG report.

Confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.3 (page 15), table 2	In the "What is the expected effect on the cost-effectiveness estimates?" row, the following sentence should have the ICER marked up as CiC: "In the analysis evinacumab is shown to generate additional costs and QALYs compared to continuation of background LLTs, leading to an ICER of [redacted] per QALY gained."	[redacted]	As per NICE's clarification, the NICE health technology manual recommends that ICERs are not marked CiC. No change required to the EAG report.
Section 1.3 (page 16), table 3	In the "What is the expected effect on the cost-effectiveness estimates?" row, the following sentence should have the ICER marked up as CiC: "The results of the EAG's analysis using the MAIC excluding lomitapide from the evinacumab arm led to an ICER of [redacted] in the south-western quadrant of the cost-effectiveness plane, meaning that lomitapide is more effective and more costly than evinacumab."	[redacted]	
Section 1.3 (page 17), table 4	In the "What is the expected effect on the cost-effectiveness estimates?" row, the following sentence should have the ICER marked up as CiC: "The EAG has provided an EAG base case cost-effectiveness	[redacted]	

	analysis comparing evinacumab to the continuation of background LLTs (with LDL apheresis) in an adult population. In the analysis evinacumab is shown to generate additional costs and QALYs comparatively to continuation of background LLTs, leading to an ICER of [redacted] per QALY gained."		
Section 1.4 (page 20), table 8	Row 3, the ICER should be marked as CiC	[redacted]	
Section 1.4 (page 21), table 9	The ICER value should be marked as CiC	[redacted]	
Section 3.2.1 (page 46), table 13	Handling of missing data row, "[redacted]. is marked as CiC when it should be AiC	[redacted]	The EAG thanks the company for highlighting this and has updated the marking to AiC.

Section 3.2.1 (page 46), table 13	Outcome assessment row, "[redacted] And "[redacted] is marked as CiC when it should be AiC	"[redacted]" And "[redacted]	The EAG thanks the company for highlighting this and has updated the marking to AiC.
Section 3.3.2 (page 52)	[redacted] is marked as CiC when it should be AiC	[redacted]	The EAG thanks the company for highlighting this and has updated the marking to AiC.

Section 4.2.7.2 (page 85), table 25	"Drug costs" under "Cost results assuming equal efficacy" to be CiC marked fully	All values to be marked fully as CiC	The EAG thanks the company for highlighting this and has updated the costs to be fully marked at CiC.
Section 4.2.10.5 (page 104)	"[redacted]" is marked as CiC when it should be AiC	"[redacted]"	The EAG thanks the company for highlighting this and has updated the marking to AiC.
Section 6.3 (page 122), table 44, scenario #3	ICER (£/QALY) value should be marked up as CiC	[redacted]	As per NICE's clarification, the NICE health technology manual recommends that ICERs are not marked CiC. No change required to the EAG report.
Section 6.3 (page 122), table 44, all scenarios	NHB values should be marked as CiC (we marked up NMB values in submission as CiC so highlighting here for consistency across documents)	All NHB values to be marked as [redacted]	The EAG considers the NHBs to be similar to ICERs for the purposes of CiC marking, therefore, these have not been marked confidential
Section 6.3 (page 122)	"In the scenarios comparing evinacumab to the continuation of LLTs, evinacumab led to additional costs and QALYs with all ICERS being between [redacted]." ICER values should be marked up as CiC	[redacted]	As per NICE's clarification, the NICE health technology manual recommends that ICERs are not marked CiC.

			No change required to the EAG report.
Section 6.3 (page 124 and 125), table 46	All ICER values and NHB values should be marked up as CiC	All values to be marked fully as CiC	As stated above, the EAG has not amended the CiC marking for NHB values.
Section 6.4 (page 128), table 48	ICER(£/QALY) value should be marked up as CiC	[redacted]	As per NICE's clarification, the NICE health technology manual recommends that ICERs are not marked CiC. No change required to the EAG report.
Section 6.4 (page 128), table 49	ICER(£/QALY) value should be marked up as CiC	[redacted]	
Section 6.5 (page 129)	"When comparing evinacumab to lomitapide the EAG found evinacumab to be less efficacious but also less costly, resulting in an ICER of [redacted], positioned in the south-west quadrant of the cost effectiveness plane. Lastly, when comparing evinacumab to LLTs, evinacumab led to additional costs and QALYs with the resulting ICER being [redacted]." – All ICER values should be marked up as CiC	[redacted] and [redacted]	

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR 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 evaluation, 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.
Technical engagement response form

NICE National Institute for Health and Care Excellence

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. 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.

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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **21 September 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 About you

Your name	[redacted] and [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Ultragenyx
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Ultragenyx is the submitting company and the manufacturer of evinacumab.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Additional key issue		
Key issue #1: Omission of continuation of background lipid lowering therapy as a comparator.	No	Background lipid lowering therapy (LLT) was not included as a comparator because the company does not regard it as an appropriate comparator. The company considers that lomitapide is the only appropriate comparator. Lomitapide can be inferred to be placed at the same position in the treatment pathway as evinacumab in the consensus statement of the European Atherosclerosis Society (EAS) of 2014 (1)*. This is clearly illustrated in Figure 9 (Section B.1.3.6, page 33) of the company submission, and is the base case used in the submission. In May 2023, during the final development of the economic model and submission dossier, the EAS consensus guidelines were updated and published (2). These now clearly place evinacumab, uniquely amongst LLT, at the same line of treatment as lomitapide (Figure 8, Section B1.3.6, page 28 of the company submission). This further cements lomitapide as the most appropriate comparator for evinacumab. It is vital to consider that in England, all adults who have not met their lipid targets with prior treatments are eligible for lomitapide through the NHS England (NHSE) commissioning policy (3). It is also important to consider that eligibility in this context is not conflated with issues due to drug intolerance, non-compliance or non-adherence. As was described in Section B.1.3.7.4 (page 35) of the company submission, lomitapide is poorly tolerated which can lead to people with HoFH stopping treatment following initiation of the drug. Very few people are ineligible for lomitapide, with only pre-existing liver disease and some (avoidable) drug-drug interactions being absolute contraindications (4). This means that at this line of therapy, either evinacumab or lomitapide

		would be initiated, and in adults, the populations eligible for treatment with both these drugs is the same. We are unaware of any example of a health technology assessment (HTA) where alternative comparators were used because of patient intolerance following initiation, despite eligibility, to the most appropriate comparator. For these reasons, it is unambiguous that lomitapide is the appropriate comparator for adults with HoFH and comparisons with background LLT are not justified. * In this key issue, the EAG also state "Additionally, the EAG considers that based on the company's restricted positioning of evinacumab as a replacement for lomitapide, evinacumab should be given after LDL apheresis in the treatment pathway." The company wishes to highlight that our analyses demonstrate that evinacumab is cost-effective with or without apheresis as a prior treatment. The base case and scenario analyses presented in the company submission, based on EAS 2014 pathways (including prior treatment with apheresis) demonstrate that evinacumab dominates lomitapide. Updated analyses based on EAS 2023 whereby evinacumab (and lomitapide) would precede LDL apheresis are presented in Table 4 of this document and confirm that evinacumab still dominates lomitapide under these assumptions.
Key issue #2: Uncertainty in the results of the matching adjusted indirect comparison for evinacumab versus lomitapide.	Yes (consideration of other efficacy estimates)	The company considers that the External Assessment Group (EAG) has used incorrect data for its base case analysis which has greatly increased the uncertainty in this parameter. We believe the choice to use the matched adjusted indirect comparison (MAIC) data with the omission of lomitapide patients is illogical and lacks robustness. The lipid lowering effect of evinacumab is not modified by lomitapide exposure: • Evinacumab and lomitapide are different types of drugs with entirely different mechanisms of action, acting on different pathways involved with lipid metabolism. Fundamentally there is no reason to believe they exhibit synergy or antagonism; that is, they are pharmacodynamically independent. • As evinacumab is a monoclonal antibody, its pharmacokinetic profile is also independent of lomitapide (lomitapide is metabolised through CYP3A4 and is an inhibitor of this isozyme). They are pharmacokinetically independent. • The independence of evinacumab and lomitapide has been partly verified through empirical research. In the ELIPSE trial (5), subgroup analysis showed the efficacy of evinacumab

		was unaffected by lomitapide. This is discussed fully in Section B.2.7.3 (page 82) of the company submission and illustrated in Figure 1. It is also worth noting that the efficacy of lomitapide was found to be independent of the use of LDL apheresis in its pivotal trial (6). This is to be expected for LLT with different mechanisms of action. • It is important to note that in all previous single technology assessments (STAs) (7-11) by NICE in this field, the concomitant use of LLT was assumed to be additive in nature, consistent with the company's current submission. Additionally, use of the MAIC that excludes lomitapide patients substantially reduces the robustness of the results: • Using the MAIC result that excludes lomitapide patients from the evinacumab arm discards 25% of the cohort enrolled in the ELIPSE study, which results in a 60% reduction in the effective sample size available in the MAIC. • Using the EAG's estimate reduces the estimated sample size (ESS) from 9.9 (*a priori* analysis) to 3.9. Not only does this discard almost all the valuable data collected by ELIPSE, it makes the value statistically unstable and introduces much more uncertainty with confidence intervals (CIs). CIs now span a range that shows evinacumab to cause a substantial LDL-C increase, to it having an efficacy of close to 100% in reducing LDL-C. This is clearly not plausible. • It is also problematic for any placebo comparisons from the ELIPSE trial as this would potentially break randomisation. Therefore, the company contends there is no logical reason to believe lomitapide is an effect modifier of evinacumab, and no rationale to prefer the subgroup MAIC over the *a priori* MAIC analysis. Furthermore, the EAG has not provided full justification for this preference. The company notes the EAG's suggested treatment effect of evinacumab [reduction in LDL-C of -33.83% (95% CI -29.17 to +96.84%)] is not reflected in <u>any other analyses, published evidence, or unpublished evidence,</u> which all suggest that evinacumab is *at least* as effective as lomitapide, and none report numerical inferiority with respect to lomitapide data compared with baseline in its pivotal trial (-40.1% LDL-C reduction, 95% CI -51.5% to -28.7%). Whilst there will never be head-to-head studies of these drugs in this population, most other estimates have found that evinacumab is numerically superior to lomitapide (illustrated in Figure 2):

		• -49.0% (95% CI -65.0 to -33.1%). Naïve data compared with placebo, ELIPSE (24 weeks, n=65). • -47.1% (95% CI -60.0 to -34.2%). Naïve data compared with baseline, ELIPSE (24 weeks, n=43). • -50.9% (95% CI -58.8 to -42.0%). Cohort with lomitapide patients removed compared with placebo, ELIPSE (24 weeks, n=51). • -46.4% (95% CI -56.4 to -36.4%). Cohort with lomitapide patients removed compared with baseline (24 weeks, n=40). • -55.08% (95% CI –71.90 to 38.27%). Full MAIC as intended *a priori* (24, weeks, ESS=9.9) [redacted] **Note** For this key issue, the EAG states the following: “Furthermore, the EAG considers this issue likely to be unresolvable based on the clinical evidence available at this time for evinacumab and lomitapide; the EAG considers that data from an adequately powered head-to-head RCT of evinacumab versus lomitapide is required.” A head-to-head trial between lomitapide and evinacumab is extremely unlikely to be conducted for methodological reasons. However, the company would like to re-affirm that the evidence for evinacumab (placebo-controlled blinded RCT at low risk of bias) is very robust for such a rare condition. In contrast, the pivotal evidence for lomitapide is weak (single-armed open-label study), with the company identifying many methodological limitations and weaknesses, which are discussed in detail the company submission in Section B.2.9.3 (pages 89-93). Therefore, the key uncertainty is related to lomitapide, not evinacumab. This concludes that the EAG’s decision to

		select the most uncertain data, and the only data favouring lomitapide, is not reasonably defendable.

Figure 1. Subgroup analysis conducted on background LLT (change from baseline LDL-C) showing no interaction between lomitapide and evinacumab.

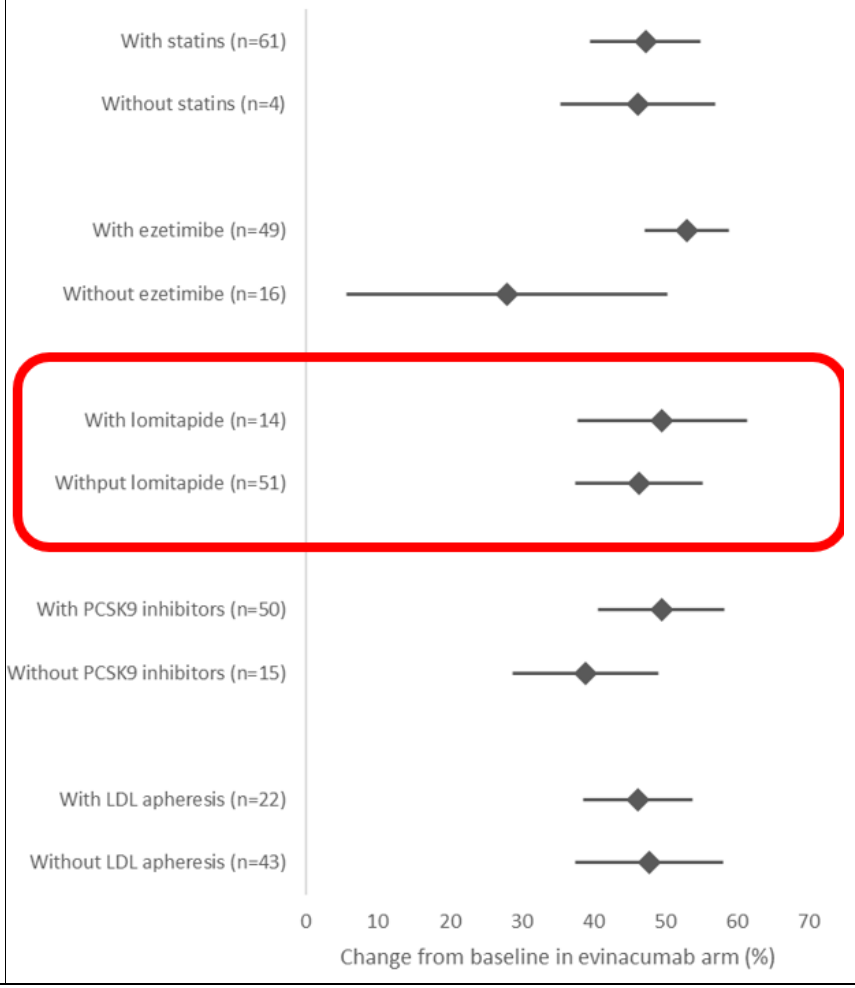
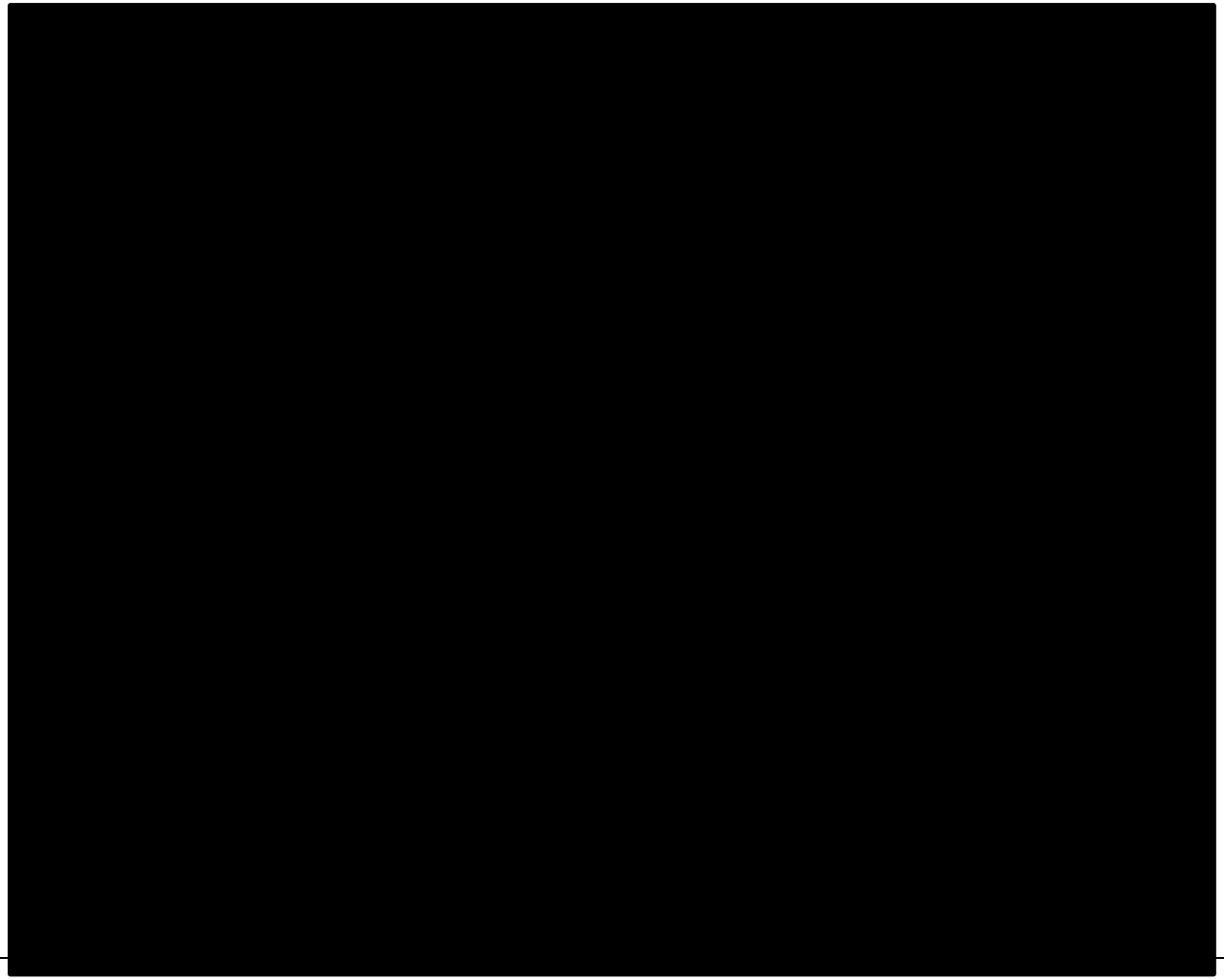


		Figure 2. Forest plot of evinacumab efficacy estimates, illustrating extreme uncertainty introduced by EAG's preferred estimate. 

Key issue #3: Omission of cost-effectiveness analysis in adolescent population.	Yes (information on lomitapide studies)	A cost-effectiveness comparison in the adolescent population was not made for 3 principal reasons: • Firstly, there was a lack of clinical data to inform this robustly, with trial R1500-CL-1719 enrolling only [redacted] adolescent patients and having no control arm (NCT03409744). Only 2 adolescent patients were enrolled into ELIPSE (5). • Secondly, the model was not designed to simulate patients at the extremes of age. Due to the rarity of the disease, some parameters needed to be extrapolated from data from the general population. For instance, in common with other models of intervention for familial hypercholesterolaemia, data from Ward *et al.* (2007) (12) was used to inform the proportion of cardiovascular events. These data are stratified by age; however the lower bound was 40 years of age, which cannot be reasonably extrapolated to adolescents. • The eligible adolescent population is extremely small, as stated in the budget impact model, this would be 5 patients per year maximum Whilst the company could not provide meaningful cost-effectiveness data in this age group, it should be borne in mind that limited clinical data from trial R1500-CL-1719 has reported evinacumab is highly effective in the adolescent population. Additionally, it is likely adolescents would benefit more than other populations due to the earlier prevention of atherosclerosis, in line with the "sooner the better" maxim (14). We believe it is imperative that adolescents have an equal right to effective treatment for HoFH as adult patients. Age is a protected characteristic (15).
Key issue #4: The model does not fully capture the health outcomes associated with secondary prevention patients.	No	The model structure was developed using concepts previously used in the context of NICE HTA submissions in similar cardiovascular conditions, including TA385 (7). This validated model structure was, in turn, based on the model presented in Ara *et al.* (2008) (16) and is frequently cited in the literature for interventions in CVD. A similar approach has also been used by Ward *et al.* (2007) (12) to inform NICE CG181 (Statins for the prevention of cardiovascular events) (17), and by Cook et al. (2004) (18). A limitation of all these state transition Markov models is that they are "memoryless" and without substantially increasing the complexity of the model, it is not feasible to represent people who have undergone multiple cardiovascular (CV) events, or events following secondary events. HoFH is an ultra-rare disease with limited available data to inform key model parameters, so it was necessary to keep the model as simple as possible to avoid unnecessary extrapolation and

		reliance on data from other conditions. In the original base case, the starting state for all patients was "stable HoFH," a state resembling stable angina requiring primary prevention. An alternative scenario whereby 50% of patients started the model in secondary prevention states was provided during the clarification process, consistent with baseline data reported in ELIPSE (5). It is noted that since this impacts both arms of the model, and the incremental QALYs, comparative to incremental costs, is not the main driver of the results. It is expected the impact of more fundamental alterations will not significantly affect ICER estimates.
Key issue #5: Cardiovascular mortality from Thompson *et al*. may not be generalisable to UK homozygous familial hypercholesterolaemia patients.	No	For the economic model to function, it is necessary to estimate the baseline risk of CV deaths and CV events over time. Because data on the natural history and prognosis of HoFH is limited, this requires the acceptance of empirical data that is less robust than is ideal, and furthermore the use of parametric modelling and extrapolation. The company accepts this limitation. The company has fully described the rationale for using the study by Thompson *et al.* (2015) (19) in Section B.3.3.3.1 (pages 125-126) of the company submission. This study was selected because it was UK-specific, HoFH-specific, and reported individual patient data (IPD) over time. Alternative baseline risks assessed by the company included the Framingham Risk Score and the QRISK3 tool, fully described in Section B.3.3.3 of the submission (page 129). In brief, these were rejected on the grounds the data were not generalisable to HoFH. This has been validated by clinical experts and was also highlighted in a previous NICE STA on familial hypercholesterolaemia (7). The EAG criticised the use of Thompson *et al.* (2015) because of differences between characteristics in patients who died and who were alive at the end of the study. A particular concern was that the cohort who died were derived from the pre-statin era. The company concedes that these are important issues and will inevitably result in some uncertainty. However, we believe these issues are mitigated through the fundamental design of the model, with the efficacy of each background LLT being applied. We consider the ELIPSE study is representative of the current treatment pathway, however, it does not provide any data to enable the estimation of cardiovascular mortality risk. And, whilst we are aware that the Thompson et al (2015) study is not entirely representative of the patient population in 2023, the model was designed to address this issue by adjusting the differences in background LLT treatment between Thompson et al. (2015) and ELIPSE. Care was taken to ensure treatment effects were being added to or subtracted from the Thompson et al (2015) cohort to reflect that in the ELIPSE cohort. The efficacy of the intervention (evinacumab) or comparator (lomitapide) were then applied to this cohort, with LLT

		being fully adjustable if necessary. This is fully described in Section B.3.3.5 of the company submission (pages 135-136). Whilst the EAG has critiqued the use the Thompson et al. (2015) study, the EAG have not suggested what alternative data could be used to assess the baseline CV risk in these patients. We believe the empirical data used (HoFH and UK specific, reporting IPD) was the most appropriate given the paucity of data available for this rare disease.
Key issue #6: Baseline LDL-C used in the model may not be representative of UK patients.	No	The EAG states the LDL-C baseline used in the model "lacks validity and is not methodologically robust." As an alternative, the EAG suggested using baseline data directly from the ELIPSE trial without adjusting background LLT differences between Thompson et al. (2015) and ELIPSE cohorts. However, we consider this raises an important issue which would distort the results and add further inaccuracy and uncertainty: • The ELIPSE trial data is not related to the Thompson et al. (2015) study which was used to derive the baseline risks, which is essential to the model. The ELIPSE study was a relatively short-term RCT (primary outcome at 24 weeks) (5) and could not be used to derive baseline CV risk. Thus, using the baseline LDL-C levels from ELIPSE causes a fundamental disconnect with the source baseline risk data and introduces additional uncertainty to the model. Considering this factor, the EAG approach of applying LDL-C data directly from the ELIPSE study and removing the background treatment adjustment (hence applying CV mortality risk derived from Thompson et al. 2015 unadjusted, see key issue 5) would introduce additional model uncertainty by overestimating the CV mortality risk, and applying a risk profile that does not correspond to the baseline LDL-C being applied in the model. Additionally, it should be noted as changing the baseline LDL-C levels would affect both arms of the model, it is anticipated the impact on ICERS would be relatively low.

Additional issues

All: Please use the table below to respond to additional issues in the EAR 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 evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Incorrect calculation by EAG of evinacumab usage (vial wastage).	Section 1.4, Table 8, page 19 Section 4.2.10.1, page 100-101 Section 4.2.10.2, page 103 Section 6.4, page 127	No	**The EAG has incorrectly calculated the number of vials required for treatment with evinacumab, double counting vial wastage. <u>This is a key issue which must be addressed</u>.** The company clearly described the calculation of the average number of vials required per patient in Section B.3.5.2 of the company submission (page 144 to 145). In their critique, the EAG opined "The EAG considers that the company's estimation of number of vials per administration is thorough but resulted in an estimate which was not whole vials (3.7 vials). The EAG considers that the calculation of vials per administration should have been rounded up to the nearest vial (four vials). The EAG ran a scenario exploring four vials per administration and results are presented in Section **Error! Reference source not found.** and this has been included in the EAG's preferred assumptions, presented in Section **Error! Reference source not found.**". **This is incorrect and the EAG have double counted vial wastage.** We believe that the EAG's approach is a mathematical error, and that the EAG are confusing the requirement for a whole number of vials at an individual level with the *mean* number of vials required to treat a group of patients. The company's approach to vial calculation was robust and based on empirical data

derived from the ELIPSE trial (5). Briefly, evinacumab is dosed at 15mg/kg and to account for the variable dosage, the mean weight of patients from ELIPSE was used, fitting the data to a log normal distribution. Using this technique, the precise number of vials required overall was calculated. Note that this base case value fully accounts for vial wastage and does not allow for vial sharing. Vial sharing was explored as scenario analysis. However, the EAG has misconstrued these calculations and opted to round up the number of vials used on average to 4, thus double counting wastage.

The calculation made by the company and EAG are reported in Figure 3. To make the point absolutely clear, a hypothetical case in which 99% of the population require 1 vial (costing £10) and 1% require 2 vials is illustrated in Figure 4. In this scenario, for 100 patients 1.01 vials would be needed per patient overall (total cost £1010). Using the EAG's method, 2 vials would be needed per patient overall (total cost £2000).

In summary, the EAG rounding up to 4 vials does not yield the cost to the NHS of providing evinacumab and is mathematically incorrect.

Figure 3. Company and EAG calculations for vial use.

Proportion of patients	Number of vials	Number of vials for costing purposes	
		Company approach	EAG approach
3.6%	6	3.65 vials	4 vials
12.5%	5		
35.9%	4		
41.5%	3		
6.5%	2		
0.0%	1		

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Figure 4. Hypothetical example of the company's and EAG's approach to vial use.
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<tr><th rowspan="2">Proportion of patients</th><th rowspan="2">Number of vials</th><th colspan="2">Number of vials for costing purposes</th></tr>
<tr><th>Company approach</th><th>EAG approach</th></tr>
<tr><td>99%</td><td>1</td><td rowspan="2">1.01 vials</td><td rowspan="2">2 vials</td></tr>
<tr><td>1%</td><td>2</td></tr>
<tr><td>Cost to treat 100 patients (£10 per vials)</td><td>99 patients * £10 + 1 patient * £20 = £1,010</td><td>£1,010</td><td>£2,000</td></tr>
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<td>Additional issue 2: Apheresis disutility</td>
<td>Section 1.4, Table 8, page 20
Section 4.2.9.3, pages 98-99
Section 4.2.9.4, page 99</td>
<td>No</td>
<td>The disutility associated with LDL apheresis calculated by the company is explained in Section B.3.4.4. (page 139) of the company submission. A disutility of -0.0171, based on estimates for disutility associated with dialysis (annual -0.164) (20) and adjusted for the proportion of time under the procedure were used. These calculations are reported in Figure 5.
In their critique, the EAG state "However, as mentioned in Section Error! Reference source not found., the company's disutility estimate reflects a monthly disutility rather than an annual estimate, as described in the CS", and provide a revised estimate of -0.205 disutility, a magnitude higher than the company's estimate. However, this is incorrect, as the company based their calculation based on the annual dialysis use, not monthly use.</td>
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Figure *5. Company calculations for disutility associated with LDL apheresis.*

	Haemodialysis	LDL-apheresis
Number of weeks	52	52
Frequency per week	3	0.5
Hours per procedure	4	2.5
Total hours per year	624	65

Time spent in LDL apheresis is 10.4% that of dialysis, resulting in an annual disutility of 0.104*0.164, equal to -0.0171.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR 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 incremental cost-effectiveness ratio (ICER)
Relating to key issue 1: order of LDL apheresis in treatment pathway	The company base case was based on the EAS 2014 consensus statement in which evinacumab and lomitapide should be given after LDL apheresis. The EAS consensus guidelines were updated in May 2023 and recommended evinacumab and lomitapide to be used before LDL apheresis.	The company has performed an additional scenario analysis to remove LDL apheresis from the background treatment options in order to reflect EAS 2023 guidelines. Evinacumab and lomitapide would be used on top of LLTs, with or without apheresis. This analysis was performed as a scenario analysis, based on the company revised base-case following the clarification question stage. Please note that this analysis is not intended to replace the company base case.	ICER: Dominant Relative change from base case incremental net monetary benefit: 1.5%

Sensitivity analyses around revised base case

The company did not revise the base case.

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3. NHS England. Clinical Commissioning Policy: Lomitapide for treating homozygous familial hypercholesterolaemia (adults NHS England) Reference: 170059P 1 2018 [Available from: https://www.england.nhs.uk/wp-content/uploads/2018/07/1679-lomitapide.pdf.

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5. Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, et al. Evinacumab for Homozygous Familial Hypercholesterolemia. N Engl J Med. 2020;383(8):711-20.

6. Stefanutti C, Blom DJ, Averna MR, Meagher EA, Theron H, Marais AD, et al. The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia - a post-hoc analysis of a Phase 3, single-arm, open-label trial. Atherosclerosis. 2015;240(2):408-14.

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11. NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [TA733]. 2021 [Available from: https://www.nice.org.uk/guidance/ta733.

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EAG additional request: patient weight data used to estimate evinacumab vials

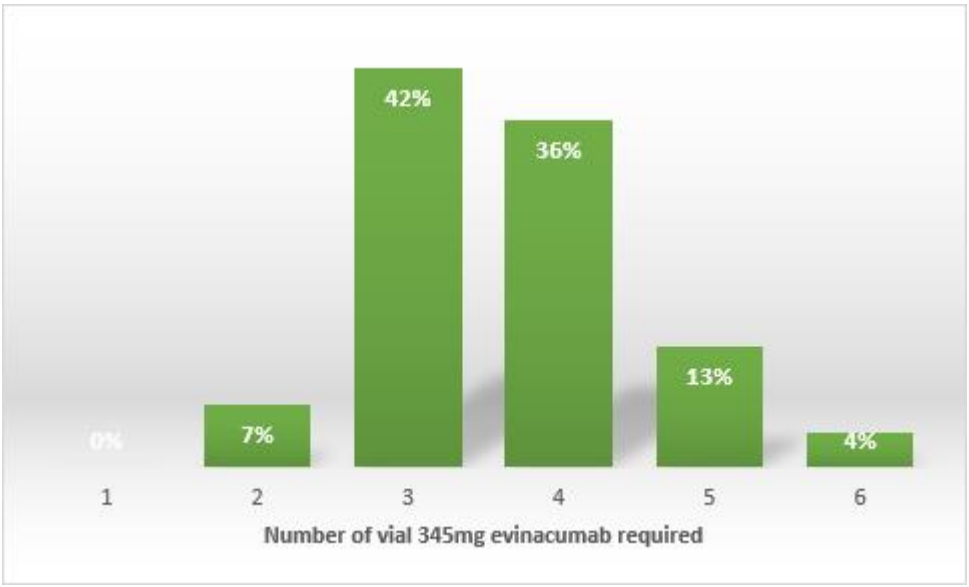
The company based their modelling calculations on the number of vials required on mean and standard deviation (SD) weight data reported in the Clinical Study Report (page 28) (1), provided to the EAG. Approach for calculations was taken based on the following rationale:

- Empirical studies have shown that body weight is not normally distributed, but right skewed (2).

- The log-normal distribution is right-skewed and closely represents the real-life distribution of body weight. There are published literature to support this assertion (3). Note that Burmaster and Crouch state in their summary conclusion that "The results are immediately useful in probabilistic (and deterministic) risk assessments".

The figure below is a graphical representation of the data used in the model. The figure shows the number of vials required reflects the distribution of weights in the ELIPSE trial in the expected way (right skewed), with no patients requiring a single vial and some obese patients requiring up to 6 vials. It is an unbiased estimate.

Figure. Distribution of vials estimated from the ELIPSE trial.



References

1. Regeneron Pharmaceuticals Inc. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia. . In: report. R-C-DNC, editor. 2019.
2. Hermanussen M, Danker-Hopfe H, Weber GW. Body weight and the shape of the natural distribution of weight, in very large samples of German, Austrian and Norwegian conscripts. Int J Obes Relat Metab Disord. 2001;25(10):1550-3.
3. Burmaster D, Crouch E. Lognormal Distributions for Body Weight as a Function of Age for Males and Females in the United States, 1976–1980. Risk Analysis. 2006;17(4):499-505.

Additional information for EAG:

From further examination of the ELIPSE IPD:

Bodyweight category	Number of vials required for each administration	Number of patients	Proportion of patients
(0 , 46kg]	2	3	5%
(46kg , 69kg]	3	29	45%
(69kg , 92kg]	4	25	38%
(92kg , 115kg]	5	5	8%
(115kg , 138kg]	6	2	3%
(138kg , 161kg]	7	1	2%
Total		65	100%

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, 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 EAR and stakeholder responses are used by the committee to help it make decisions at the 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 for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

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 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. 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.

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. 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.

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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **21 September 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

NICE National Institute for Health and Care Excellence

Part 1: Treating homozygous familial hypercholesterolaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	JAIMINI CEGLA
2. Name of organisation	IMPERIAL COLLEGE HEALTHCARE NHS TRUST
3. Job title or position	CONSULTANT IN METABOLIC MEDICINE, CLINICAL LEAD FOR THE LIPIDS AND CARDIOVASCULAR RISK SERVICE
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 homozygous familial hypercholesterolaemia ? ☐ A specialist in the clinical evidence base for homozygous familial hypercholesterolaemia 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 ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
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.	NONE

8. What is the main aim of treatment for homozygous familial hypercholesterolaemia ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent premature cardiovascular disease leading to early heart attacks and stroke and allow patients to enjoy good quality of life for as long as possible.
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)	reducing LDL cholesterol and thereby reducing risk for progressive cardiovascular disease. Ideally targeting the LDL cholesterol below 1.8 mmol per litre
10. In your view, is there an unmet need for patients and healthcare professionals in homozygous familial hypercholesterolaemia?	I am in no doubt that there is an unmet need for these patients as I see this in my clinical practise on a daily basis. These patients and their families suffer with premature death, premature cardiovascular disease, having seen siblings suffer with premature cardiovascular disease or death, saying their children suffer with the same condition. Despite advances in the field, the vast majority of patients are not achieving ideal LDL cholesterol targets.
11. How is homozygous familial hypercholesterolaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Most clinicians looking after these patients in the UK use the Heart UK consensus statement and the EAS guidance. Due to the rarity of the condition there are only five to six centres around the UK that look after these patients. Through heart UK there are good opportunities for collaborating and sharing experience. This has allowed for harmonisation of care across the UK. The new technology would be transformative to the lives of patients with homozygous FH. For those who cannot tolerate lomitapide due to liver and other side effects, this could be another option. The use of aphereis is limited as it comes with a huge burden on the patient and issues around access geographically.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	this technology is not currently available in HS practice

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	the technology will be used in patients in whom the current therapies are not adequately achieving clinical efficacy. Specialist clinic it should be prescribed by the apheresis services as they have specialist nurses and expertise in providing intravenous therapies. They also have expertise in treating the condition.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	This treatment will be life changing for certain patients. But for those who cannot tolerate lomitapide and apheresis, this treatment will help achieve LDL cholesterol lowering to target. If the treatment is available for patients to have at home once several doses have been given in a hospital setting, this will further improve patient's quality of life. Currently apheresis requires a full day in hospital on a weekly basis and this is a real burden for these young patients
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Treatment is effective in all types of homozygous FH.
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)	this will be easier to use for some patients than lomitapide if they cannot tolerate it. From a practical perspective this will be less time consuming than apheresis,

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This treatment will be much more acceptible to patients than apheresis, although this will still remain an option. This could be used with or without lomitapide.
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	other health benefits could be: 1. not having to come to hospital for a full day on a weekly basis 2. not requiring a a fistula 3. psychological benefits knowing that the LDL is lower and therefore risk of progression is lower
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? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology is a step change and has huge prospect to improve the lives of our patients we have several patients who can tolerate neither apheresis nor lomitapide. These patients now have another option.
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?	Side effects are negligible
20. Do the clinical trials on the technology reflect current UK 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?	Important outcome of the trials would be CVD risk reduction however this is impossible given the rarity of the condition. Therefore the trials correctly used LDL cholesterol as a surrogate marker. The trials do reflect clinical practice in the UK

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not 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
23. How do data on real-world experience compare with the trial data?	this compares well and is reassuring: The LDL-C lowering effect of evinacumab without LA were also investigated in the 7 HoFH patients after a subsequent compassionate extension period. Twenty-four months of treatment with evinacumab against background LA and LLT resulted in a significant reduction in LDL-C (−46.8%; $p < 0.001$). LDL-C reduction with evinacumab was maintained during the compassionate extensions period in the absence of treatment with LA (−43.4%; mean follow-up of 208 ± 90 days). Evinacumab was well-tolerated, with no major adverse event reported or significant changes in liver and muscle enzyme concentrations. Our findings suggest that evinacumab is a safe and effective treatment for patients with HoFH receiving best standard of care in a routine setting. Pharmaceuticals (Basel) • • • . 2022 Nov 11;15(11):1389. doi: 10.3390/ph15111389.

	Long-Term Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia: Real-World Clinical Experience
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	It is important to start treating homozygous FH from birth therefore I support the potential use of this technology from the age of 12. Adolescence is a key time when LDL cholesterol levels rise and important to mitigate. Given the severity of the condition I believe the benefit of the drug outweighs any risk from the limited evidence in this cohort.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, 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 committee meeting.

For information: the professional organisation that nominated you has also 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 EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue #1: Omission of continuation of background lipid lowering therapy as a comparator. • *What treatment would people who cannot have lomitapide be offered in clinical practice? How commonly do*	For patients who cannot tolerate lomitapide, there are no other options. 50% of my patients have stopped limit applied due to toxicity/tolerability. Further therapy would be always used adjunctively

people stop lomitapide due to toxicity issues? • *Would people whose disease does not respond to standard first- and second-line lipid lowering therapy ever stop these treatments or would further therapy always be used adjunctively?* • *Would LDL apheresis ever be used at the same point in the pathway as evinacumab?*	LDL apheresis and *evinacumab maybe used concomitantly. This would indeed work quite well as the patient could have their infusion of evinacumab after their apheresis session*
Key issue #2: Uncertainty in the results of the matching adjusted indirect comparison for evinacumab versus lomitapide.	
Key issue #3: Omission of cost-effectiveness analysis in adolescent population. • *What treatment would adolescents with homozygous familial hypercholesterolaemia have in clinical practice when their LDL-C value has not responded to standard first- and second-line lipid lowering therapies?* • *What proportion of people with homozygous familial hypercholesterolaemia are diagnosed under 18 years old?*	There are no other options for these patients. The vast majority of patients are diagnosed under the age of 18 as they have florid clinical signs. Occasionally they are missed and picked up only after a cardiac event.

Key issue #4: The model does not fully capture the health outcomes associated with secondary prevention patients. • *How would short- and long-term outcomes differ for people having an acute secondary cardiovascular event from those having a first acute cardiovascular event?*	It is not correct to consider primary and secondary prevention as binary outcomes. This is a continuum. Even if a patient has not had a heart attack they will undoubtedly have atherosclerotic disease and should be treated aggressively.
Key issue #5: Cardiovascular mortality from Thompson *et al*. may not be generalisable to UK homozygous familial hypercholesterolaemia patients. • *How has treatment for homozygous familial hypercholesterolaemia changed in the past 10 years? Would you expect improvements in cardiovascular mortality with newly available treatments?* • *Are the background treatments used in Thompson et al. generalisable to current practice?*	The main changes are availability of lomitapide and PCSK9i although the latter do not have great efficacy in the majority of homozygous patients. These will have improved cardiovascular mortality in some patients. However half of the patients do not tolerate lomitapide. The background treatments are generalizable.
Key issue #6: Baseline LDL-C used in the model may not be representative of UK patients.	The study was done in UK patients so why would the baseline LDL not be representative?
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Despite current therapies, the vast majority of homozygous FH patients do not achieve currently recognised LDL targets

This results in premature cardiovascular disease and death

The availability of evinacumab will be transformative for these patients.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the 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 about living with homozygous familial hypercholesterolaemia or caring for a patient with homozygous familial hypercholesterolaemia. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.1).

A patient 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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

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Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **21 September 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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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.

Part 1: Living with this condition or caring for a patient with homozygous familial hypercholesterolaemia

Table 1 About you, homozygous familial hypercholesterolaemia, current treatments and equality

1. Your name	Karen Hasid
2. Are you (please tick all that apply)	☐ A patient with homozygous familial hypercholesterolaemia? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with homozygous familial hypercholesterolaemia? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	HEART UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with homozygous familial hypercholesterolaemia? **If you are a carer (for someone with homozygous familial hypercholesterolaemia) please share your experience of caring for them**	As a mum of two boys, both with the condition I can only describe the journey as a rollercoaster. After two years and an immense battle, I finally got a diagnosis. Throughout this period, I was called a neurotic mum, I was told to go home and pop a xanthoma on my son's arm, then we got a misdiagnosis of a rare eye condition from another consultant. It wasn't until I paid to see a private paediatric dermatologist who finally listened to me, took me seriously and our medical history (both my mother-in-law and husband have FH.) From this point we have been well cared for at the Metabolic centre in Manchester's children's hospital where we have had the right care. This doesn't go without challenges themselves. Liver functions not so good due to all the medications and prior to this being asked to meet with transplant specialists. Having children growing up with this condition teaching them to eat right is difficult plus ensuring that they take their medication daily.
7a. What do you think of the current treatments and care available for homozygous familial hypercholesterolaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Current treatment wise, I have one son who has been on Repatha for the past several years. (He was unable to tolerate Atorvastatin and now takes Rosuvastatin but did not see a reduction as good as my eldest son on Atorvastatin.) My eldest who is nearly 18, I have had to battle to get him the injection as he was a couple of points below the threshold. This child has taken Atorvastatin 80mg alongside with Ezetimibe for many years. I have found this to be very frustrating as knowing there is an alternative out there that perhaps could have allowed him to lower his numbers and even drop his Atorvastatin dose as his liver function has been affected.
8. If there are disadvantages for patients of current NHS treatments for homozygous familial hypercholesterolaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I feel for HOFH patients, when looking at new drugs and having such a rare form the whole patient's medical history should be taken into consideration and not just the overall cholesterol LDL number. Over the years I have had discussions with regards to apheresis, even liver transplants, however I felt this was not suitable for my children. If only my son was given the opportunity to take Repatha earlier this

	would have saved time and effort of the doctors and perhaps helped with his liver function. Another point I would like to raise is with regards to my eldest son. As reaches 18 I am also highly concerned on the level of care in the adult hospital. I haven't had an appointment or follow up since pre covid. We have discussed transition but are yet to meet since this was brought to my attention early at the start of 2023.
9a. If there are advantages of evinacumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does evinacumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	The advances are excellent its just getting the drugs to the right patients. I appreciate cost is a factor but when you have rare genetics and have so many daily challenges with food medication liver conditions etc… I would hope they would be prescribed new advanced drugs to give the patient a better quality of life and not just necessarily on LDL numbers**.** With regards to the benefits as discussed in my previous points
10. If there are disadvantages of evinacumab over current treatments on the NHS please describe these. For example, are there any risks with evinacumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	n/a
11. Are there any groups of patients who might benefit more from evinacumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	n/a

12. Are there any potential equality issues that should be taken into account when considering homozygous familial hypercholesterolaemia and evinacumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	n/a
13. Are there any other issues that you would like the committee to consider?	n/a

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also 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 EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue #1: Omission of continuation of background lipid lowering therapy as a comparator. • *Please describe your experience with lomitapide (if relevant). Did you or the person you care for experience side effects?*	We consider patient perspectives may particularly help to address this issue
Key issue #2: Uncertainty in the results of the matching adjusted indirect comparison for evinacumab versus lomitapide.	

Key issue #3: Omission of cost-effectiveness analysis in adolescent population**.** • *At what age were you or the person you care for diagnosed?* • *If diagnosed under the age of 18, what treatments were you or the person you care for offered?*	We consider patient perspectives may particularly help to address this issue
Key issue #4: The model does not fully capture the health outcomes associated with secondary prevention patients.	
Key issue #5: Cardiovascular mortality from Thompson *et al*. may not be generalisable to UK homozygous familial hypercholesterolaemia patients.	
Key issue #6: Baseline LDL-C used in the model may not be representative of UK patients.	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR 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 evaluation, 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.

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. 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.

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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **21 September 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	BCS
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**NA**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**NA**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue #1: Omission of continuation of background lipid lowering therapy as a comparator.	NA	No opinion
Key issue #2: Uncertainty in the results of the matching adjusted indirect comparison for evinacumab versus lomitapide.	No	Lomitamide causes marked GI disturbance and an increase in liver fat as the partciles which become LDL P don't get assembled and don't leave the liver.
Key issue #3: Omission of cost-effectiveness analysis in adolescent population.	NA	No opinion
Key issue #4: The model does not fully capture the health outcomes associated with secondary prevention patients.	No	Routine practice is statins and ezetimibe. LDL-C median no treatment is 14.5mmol/L range. Woth statins and ezetimibe might get this to 8. Some may respond to PCSK9 Mab (cheaper than evinacumab) if there is some LDLR function. Most with resistant LDL-C have little or no LDLR function so need another option. Evinacumab doesn't work through the LDL-R and its efficacy is significant even in null nulls so this is a real step up in what we can do for patients.
Key issue #5: Cardiovascular mortality from Thompson *et al*.	No	This study was by a UK research group, predominantly looking at UK patients. It is generalisable to the wider UK population of interest.

may not be generalisable to UK homozygous familial hypercholesterolaemia patients.		
Key issue #6: Baseline LDL-C used in the model may not be representative of UK patients.		See above

Additional issues

All: Please use the table below to respond to additional issues in the EAR 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 evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
BCS feel the new treatment is safe	Please indicate the section(s) of the EAR that discuss this issue	NO	It would replace apheresis which is miserable for patients with few centres. Apheresis is weekly ideally but rationed every two weeks. This is a 1 hr Iv infusion monthly.

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Technical engagement response

September 2023

Source of funding

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1 Introduction

This document provides the External Assessment Group's (EAG's) critique of the company's response to technical engagement (TE) for the appraisal of evinacumab for treating homozygous familial hypercholesterolaemia (HoFH) in people aged 12 years and over [ID2704]. Each of the key issues outlined in the TE report are discussed in detail in Section 3, with additional issues raised by the company discussed in Section 4. For a summary of the EAG's judgement on each key issue, see Table 1. The EAG reports in Section 2 their original base case findings in addition to the corrected and updated EAG base cases following the company's TE response.

Table 1. Issues for TE and current status regarding issue resolution

Key issue		Status according to the EAG	Company approach	EAG approach
1	Omission of continuation of background LLT as a comparator.	Unresolved	The company does not regard continuation of background LLT an appropriate comparator.	The EAG considers continuation of background LLT to be a comparator for both the adolescent and adult populations and that the trial results from the DBTP of ELIPSE could inform this comparison.
2	Uncertainty in the results of the matching adjusted indirect comparison for evinacumab versus lomitapide.	Unresolved (considered unresolvable due to data limitations)	The company considers the MAIC including patients on background lomitapide in the evinacumab arm is more robust than the MAIC where evinacumab patients on background lomitapide are removed.	The EAG considers the MAIC results to be highly uncertain due to the poor overlap between studies (as indicated by the low resulting effective sample sizes), and considers both MAIC results (with or without background lomitapide) not to be unreasonable based on the limited data available. However, the EAG considers the MAIC without background lomitapide to more closely represent the population for the company's proposed positioning of evinacumab in the treatment pathway, particularly given

				lomitapide is the comparator in the ITC.
3	Omission of cost-effectiveness analysis in adolescent population.	Unresolved. Additional scenario conducted by the EAG.	No cost-effectiveness analysis presented for the adolescent population	The EAG considers the company should present an analysis of cost-effectiveness using data for a relevant comparator for the adolescent HoFH population.
4	The model does not fully capture the health outcomes associated with secondary prevention patients.	Unresolved. Additional scenario conducted by the EAG.	The company considers the modelling approach is appropriate	The EAG considers that given the majority of the patients in ELIPSE had a case history of CV events the model should account for the key HRQoL differences between primary and recurrent CV events.
5	CVM from Thompson *et al.* may not be generalisable to UK HoFH patients.	Unresolved. Additional scenario conducted by the EAG.	The company considers their modelling approach mitigates the uncertainty introduced by the Thompson *et al.* study.[1]	The EAG considers that the company should conduct further sensitivity analyses around the CV mortality from Thompson *et al.* [1]
6	Baseline LDL-C used in the model.	Unresolved. Additional scenario conducted by the EAG.	The company considers that baseline LDL-C from Thompson *et al.* should be used as and adapted to reflect ELIPSE as Thompson *et al.* informs baseline risk in the model. [1]	The EAG considers that the company approach to adapting the Thompson baseline to ELIPSE introduces considerable uncertainty and is inappropriate given the available trial data from ELIPSE.

Abbreviations CV, cardiovascular; CVM, cardiovascular mortality; EAG, External Assessment Group; HoFH, homozygous familial hypercholesterolaemia; ITC, indirect treatment comparison; LDL-C, low density lipoprotein cholesterol; LLT, lipid lowering therapy; MAIC, matching adjusted indirect comparison.

2 EAG base case corrections and updates

The EAG thanks the company for highlighting the issues with incorporating the EAG assumptions outlined in the EAG report. Following their comments, the EAG has corrected the original EAG base cases (Table 2), to adjust for the correct value of apheresis disutility (Table 3).

Additionally, the EAG has adapted their assumed treatment effects for evinacumab and lomitapide. In the company's submission, and followed through in the EAG report, the evinacumab treatment effect was calculated relative to lomitapide using a MAIC. However, the EAG considers that the uncertainty represented in the indirect comparison should be associated with the treatment effect of lomitapide (as the purpose of the indirect comparison is to obtain this estimate) rather than the treatment effect of evinacumab (which is directly observed in ELIPSE). As such, the EAG has calculated the treatment effect of lomitapide relative to the evinacumab treatment effect measured in ELIPSE. This approach also ensures that a consistent treatment effect for evinacumab is used when comparing against LLTs and/or lomitapide.

The treatment effect for lomitapide was calculated by applying the mean difference in LDL-C reduction from evinacumab from the company's MAIC (Table 17 in the EAG report) to the treatment effect of evinacumab observed in ELIPSE (47.1%). Using this approach, the lomitapide treatment effect was adjusted from 40.1% to 32.12% or 53.37% depending on which MAIC results were used. The corrections to the EAG base case when including these data transformations are outlined in Table 4.

Table 2. EAG base cases from the EAG report

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Evinacumab vs lomitapide, MAIC excluding lomitapide treated evinacumab patients									
Lomitapide	5,700,073	12.20	8.73	-	-	-	-		
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs lomitapide, MAIC including lomitapide treated evinacumab patients									
Lomitapide	5,700,073	12.20	8.73	-	-	-	-		
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs LLTs									
LLTs	262,092	11.16	7.98	-	-	-	-		

Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

Table 3. Corrected EAG base case – correcting apheresis disutility

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Evinacumab vs lomitapide, MAIC excluding lomitapide treated evinacumab patients									
Lomitapide	5,700,073	12.20	8.73	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs lomitapide, MAIC including lomitapide treated evinacumab patients									
Lomitapide	5,700,073	12.20	9.47	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs LLTs									
LLTs	262,092	11.16	8.65	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

Table 4. Corrected EAG base case – anchoring treatment effects to evinacumab from ELIPSE

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 TWP)
Evinacumab vs lomitapide, MAIC excluding lomitapide treated evinacumab patients									
Lomitapide	5,830,021	12.48	8.94	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs lomitapide, MAIC including lomitapide treated evinacumab patients									
Lomitapide	5,615,094	12.01	8.60	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs LLTs									
LLTs	262,092	11.16	7.98	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

2.1 Updated EAG base case as a result of Technical Engagement

Given the company's TE response to key issue 5, the EAG agrees with the company that the EAG's preferred approach creates a disconnect between the source baseline risk, which stems from Thompson *et al.* with a baseline LDL-C of 8.7 mmol/L, and the EAG preferred baseline LDL-C from the ELIPSE trial which was 6.6 mmol/L. [1]

Additionally, during TE process the company was able to provide the observed evinacumab treated patients weights from ELIPSE. Following this additionally information the EAG has updated the mean number of vials used per administration, while accounting for wastage, from 4 to 3.65. Based on the observed data, the EAG now considers 3.65 vials to appropriately account for wastage.

The EAG has updated their base case to reflect these changes (Table 5) with the methodology outlined in Section 3.6 and 4.1 respectively.

Table 5. EAG's updated base case

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Evinacumab vs lomitapide, MAIC excluding lomitapide treated evinacumab patients									
Lomitapide	6,280,717	13.46	10.45	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs lomitapide, MAIC including lomitapide treated evinacumab patients									
Lomitapide	6,159,653	13.19	10.25	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs LLTs									
LLTs	289,472	12.68	9.85	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

3 Issues for Technical Engagement

3.1 Key issue 1: Omission of continuation of background LLT as a comparator

The EAG notes that no new evidence has been presented by the company in response to technical engagement and that the company still considers lomitapide to be the only relevant comparator for adults with HoFH. The EAG considers that while lomitapide (with or without LDL apheresis) is a key comparator for the adult population, continuation of background LLTs (without lomitapide) is also a relevant comparator for those patients unsuitable for lomitapide. The EAG is concerned that in clinical practice there may well be a population that clinicians would want to treat with lomitapide, but are unable to for various reasons such as toxicity concerns, that continue on LLTs as standard practice. This is of particular importance as lomitapide has not been subject to a NICE appraisal and so a conclusion that evinacumab is cost-effective compared to lomitapide does not automatically mean evinacumab is cost-effective compared to LLTs.

In addition, the EAG considers that continuation of maximally tolerated background non-lomitapide LLTs is potentially the main comparator for evinacumab in the adolescent population based on the company's proposed positioning for evinacumab.

In the EAG report, the EAG provided an EAG base case cost-effectiveness analysis comparing evinacumab to the continuation of background LLT (with LDL apheresis). In the analysis, evinacumab is shown to generate additional costs and QALYs compared to continuation of background LLTs, leading to an ICER of £3,336,965 per QALY gained.

3.2 Key issue 2: Uncertainty in the results of the matching adjusted indirect comparison for evinacumab versus lomitapide

The company conducted a matched adjusted indirect comparison (MAIC) to compare evinacumab with lomitapide but the EAG is concerned that 25.6% of patients in the evinacumab arm of ELIPSE received background therapy with lomitapide (n=11), which could potentially confound the results of the MAIC as background therapies were not considered as part of the matching process. The EAG therefore considers that the removal of the patients on background lomitapide from the evinacumab arm more closely reflects the company's proposed positioning of evinacumab in the treatment pathway for HoFH.

The EAG notes that the company considers the exclusion of patients on lomitapide in the evinacumab dataset reduces the robustness of the results. The company also highlighted that evinacumab and lomitapide have different mechanisms of action and that previous single technology assessments (STAs)[2-6] by NICE have assumed that the concomitant use of lipid lowering therapies (LLT) was additive. In addition, the company considered that subgroup analysis in the ELIPSE trial[7] demonstrated that the efficacy of evinacumab was unaffected by lomitapide. Due to time constraints the EAG has not reviewed all previous STAs but the EAG is concerned that the ELIPSE trial was not adequately powered to detect between subgroup differences in efficacy based on prior LLT. The EAG thus recommends caution in drawing conclusions based on these subgroup results.

The EAG acknowledges that the exclusion of the lomitapide patients from the evinacumab arm of the ELIPSE trial in the MAIC reduces the effective sample size from 9.9 to 3.9 and results in greater uncertainty as demonstrated by the wider 95% confidence intervals. In response to TE the company has presented a forest plot summarising the percentage change from baseline in LDL-C results for evinacumab from various different analyses using the ELIPSE data (Figure 1). The EAG notes that the efficacy of evinacumab varies from [redacted] across these analyses and that in both the MAIC with lomitapide and without lomitapide patients the 95% CIs are wide:

- -33.83% (95% CI -29.17 to +96.84%). MAIC with lomitapide patients removed (24, weeks, ESS 3.9);
- -49.0% (95% CI -65.0 to -33.1%). Naïve data compared with placebo, ELIPSE (24 weeks, n=65);
- -47.1% (95% CI -60.0 to -34.2%). Naïve data compared with baseline, ELIPSE (24 weeks, n=43);
- -50.9% (95% CI -58.8 to -42.0%). Cohort with lomitapide patients removed compared with placebo, ELIPSE (24 weeks, n=51);
- -46.4% (95% CI -56.4 to -36.4%). Cohort with lomitapide patients removed compared with baseline (24 weeks, n=40);
- -55.08% (95% CI –71.90 to 38.27%). Full MAIC as intended a priori (24, weeks, ESS=9.9);

[redacted]

Figure 1. [redacted]

[redacted]

The EAG notes that in the MAICs, the company has applied the adjustment to the evinacumab arm and thus the efficacy of evinacumab differs depending on which MAIC is selected (Table 6). As discussed in Section 2, the EAG has revised the EAG base case to reflect the efficacy of evinacumab as seen in ELIPSE (47.1% reduction in LDL-C) and used the MAIC to estimate the efficacy of lomitapide. This results in an efficacy of lomitapide of 32.12% reduction in LDL-C in the MAIC with lomitapide patients included and 53.37% reduction in LDL-C in the MAIC with lomitapide patients excluded. The EAG notes that in the unadjusted naïve ITC reported in Table 6, evinacumab is reported to be associated with a -47.24% reduction in LDL-C, whereas in the primary publication of ELIPSE evinacumab is associated with a 47.1% reduction in LDL-C. The EAG is unclear as to the reason for this discrepancy in LDL-C reduction and has used the result from the primary publication of ELIPSE in the EAG base case (47.1%). Results of the updated EAG base case are presented in Section 2.

Table 6. Results of the MAIC for mean difference in percentage change in LDL-C from baseline for evinacumab vs lomitapide (adapted from CS Table 21 and CQ response appendix for question A16)

Method	Matching variables	Evinacumab n/ESS	Lomitapide n	Mean (95% CI) evinacumab	Mean (95% CI) lomitapide	Mean Difference (95% CI) evinacumab vs lomitapide
Including patients receiving lomitapide						
Unadjusted Naïve ITC	NA	43.0	29.0	-47.24 (-56.18 to -38.31)	-40.1 (-51.47 to -28.73) [a]	-7.14 (-21.91 to 7.63)
MAIC	Age, CHD, LDL-C	9.9	29.0	-55.08 (-71.90 to -38.27)	-40.1 (-51.47 to -28.73) [a]	-14.98 (-36.76 to 6.80)
MAIC (sensitivity analysis)	Age	23.6	29.0	-56.40 (-64.66 to -48.14)	-40.1 (-51.47 to -28.73) [a]	-16.3 (-30.72 to -1.88)*
Excluding patients receiving lomitapide						
Unadjusted naïve ITC	NA	32.0	29.0	-46.42 (-57.62 to -35.23)	-40.1 (-51.47 to -28.73) [a]	-6.32 (-22.7 to -9.63)
MAIC	Age, CHD, LDL-C	3.9	29.0	-33.83 (-96.84 to 29.17)	-40.1 (-51.47 to -28.73) [a]	6.27 (-26.1 to 38.64)
MAIC (sensitivity analysis)	Age	16.7	29.0	-54.94 (-65.16 to -44.72)	-40.1 (-51.47 to -28.73) [a]	-14.84 (-30.08 to 0.4)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; ESS, effective sample size; ITC, indirect treatment comparison; LDL-C, low-density lipoprotein cholesterol; MAIC, matching-adjusted indirect comparison; n, number of patients.

[a] Data presented to no decimal places to reflect the reporting style by Cuchel *et al.* 2013.

*Evinacumab was statistically superior to lomitapide when the evinacumab cohort was matched for age.

The EAG considers the results from the MAICs to be uncertain, principally due to poor matching between the studies, which is exacerbated by the limited reporting of baseline characteristics from Cuchel *et al.* 2013 and the small number of patients included in each study. However, the EAG considers that it would not be unreasonable to interpret the results as a lack of evidence to suggest a substantial difference in LDL-C reduction with evinacumab and lomitapide. Given the conflicting results from the two possible MAICs, the EAG conducted a cost-minimisation analysis between evinacumab and lomitapide as a scenario (reported in Table 25 of the EAG report), which found evinacumab to be cost saving compared to lomitapide. However, the EAG considers that the lack of robust evidence to inform an ITC should not be misinterpreted as evidence of equivalence between

the evinacumab and lomitapide, and so the results of the cost-minimisation analysis should be interpreted with caution.

3.3 Key issue 3: Omission of cost-effectiveness analysis in adolescent population

The company reported that they have not conducted an analysis of cost-effectiveness in the adolescent population for three reasons:

1) Lack of clinical data;
2) Model design and parameters not being suitable for adolescent population;
3) Small eligible population calculated in the company budget impact model.

The EAG acknowledges the company's views but nevertheless is concerned that the key comparator for evinacumab in the adolescent population is continuation of background LLTs and that lomitapide is not a treatment option for adolescents.

[redacted] in the adolescent population with appropriately adjusted baseline characteristics and inputs for an adolescent population in the economic model. The EAG has conducted an exploratory cost-effectiveness analysis as an illustrative example with results presented below. The EAG stresses the illustrative nature of this scenario, as it only makes use of the data available to the EAG at this time. The EAG considers that a more robust comparison could be provided by the company using more appropriate data.

The scenario analyses in Table 7 report the cost effectiveness of evinacumab against lomitapide and LLTs and lomitapide in an adolescent population using the alternative MIAC results. The EAG notes that due to the lack of trial specific data for adolescents, LLTs, evinacumab, and lomitapide treatment effects for adults were assumed in proxy. Additionally, as outlined by the company in the

CS, the data from Ward *et al.* used to derive non-fatal CV event rates has a starting age of 40 years old.[8] Therefore, CV risks in the scenario are more specific to those considerable older than 12 years old and are likely greatly overestimated.

To conduct the scenario, the model was used to compare LLTs to evinacumab from 12 years old over a lifetime horizon. Next LLTs were compared to evinacumab from 12 to 17 years old, and lomitapide to evinacumab from 18 years to over a time life horizon, with a discount rate reflecting five years in the model applied to the first cycle when comparing to lomitapide. The results comparing evinacumab to LLTs from 12 to 17 and evinacumab to lomitapide were summed to estimate the total costs and QALYs for the adolescence lomitapide treatment arm. Results of the scenario are outlined in Table 7. However, once adolescents become adults, the same issue previously stated by the EAG becomes important – that is, the population that clinicians might want to treat with lomitapide but are unable to. As such, the EAG considers LLTs an appropriate comparator to evinacumab in the adolescent population; the cost effectiveness estimates comparing LLTs to evinacumab for the adolescent population are presented in Table 7.

Table 7. Adolescent population scenario, 12 years old to lifetime horizon

Intervention	Total Costs (£)	Total QALYs	inc. costs	inc. QALYs	ICER	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Using MAIC treatment effects excluding lomitapide treated evinacumab patients							
LLTs & lomitapide	£7,311,558	17.78					
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using MAIC treatment effects including lomitapide treated evinacumab patients							
LLTs & lomitapide	7,226,704	17.63	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELIPSE treatment effects							
LLTs	433,166	17.31					
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

3.4 Key issue 4: The model does not fully capture the health outcomes associated with secondary prevention patients.

The EAG notes that no model update has been presented by the company in response to technical engagement and that the company still considers the model appropriate. As outlined in the EAG report, given that the majority of patients in ELIPSE, the source of the efficacy data for evinacumab, have had one or more recurrent CV events and robust data exists highlighting the key differences in experiencing CV successive events, the EAG considers it a critical oversight by the company not to fully capture these differences in the model.

The company states that it is not feasible to represent patients who have undergone recurrent CV events due to the "memoryless" properties of Markov models. The EAG considers that this obstacle could have been easily overcome by changing the structure of the model and that developing a model mirroring that of NICE TA694, which assessed bempedoic acid with ezetimibe for treating primary hypercholesterolaemia, would have made this feasible.[9]

As a scenario, the EAG modelled a cohort of secondary prevention patients. All patients enter the model in the Stable HoFH health states whose health state utility and baseline risk has been adapted to those of secondary prevention patients. Utility and risk for the Stable HoFH were calculated using a weighted average of the post-event health states in the "primary prevention" base case model. Acute and post event health states utilities for recurrent CV events were informed using those reported by Ara and Brazier (Table 8).[10] As acute and post-event utilities for TIA were the same in the company model they have remained the same in the EAG scenario but have been limited to the utility of the Stable HoFH health state. The results of the scenario with the EAG base case assumptions are outlined in Table 9.

Table 8. Base case and secondary prevention cohort scenario health state utility values

Health state	Base case utilities used in the model			Secondary prevention and successive event utilities scenario*		
	Baseline utilities in the model	Acute CV event (event < 12 months, history of just event)	Post CV event (no event < 12 months, history of event)	Baseline utilities in the scenario	Acute CV event (event <12 months, history of event + other cv condition)	Post CV event (no event <12 months, history of event + other CV condition)
Stable HoFH	0.891	-	-	0.749	-	-

Angina	-	0.615	0.775	-	0.541	0.715
Unstable angina	-	0.615	0.775	-	0.541	0.715
MI	-	0.721	0.742	-	0.431	0.685
TIA	-	0.760	0.760	-	0.749	0.749
Stroke	-	0.626	0.668	-	0.479	0.641

Abbreviations: CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack.

*Stable HoFH utilities reflect the secondary prevention patient utilities, calculated using a weighted average of the post-event health states in the base case model.

Table 9. EAG scenario assuming all patients are secondary prevention

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Evinacumab vs lomitapide, MAIC excluding lomitapide treated evinacumab patients									
Lomitapide	6,234,119	13.35	9.26	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs lomitapide, MAIC including lomitapide treated evinacumab patients									
Lomitapide	6,113,846	13.09	9.07	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs LLTs									
LLTs	289,080	12.58	8.69	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

3.5 Key issue 5: CVM from Thompson *et al.* may not be generalisable to UK HoFH patients

In the EAG report it was suggested that at TE the company conducted additional sensitivity analysis around the baseline risk in the model, which was informed by Thompson *et al.*, given the potential flaws of the study as outlined in the EAG report.[1] The company did not conduct the sensitivity analysis as suggested, stating that the issues introduced with using CV mortality from Thompson *et al.* were mitigated with the company preferred approach of applying the individual LLT efficacies to the Thompson *et al.* baseline LDL-C in the same proportion of patients on specific LLTs in ELIPSE. [1]

The EAG considers this approach does little to reduce the uncertainty introduced by the Thompson *et al.* study and that the company's preferred approach is not robust in aligning the Thompson *et al.*

baseline LDL-C to that of ELIPSE and therefore does not correctly adjust baseline risk from Thompson *et al.* to that of patients in ELIPSE. This is perhaps most clearly seen when comparing LDL-C baselines between the company's approach and ELIPSE, with ELIPSE baseline being 6.6mmol/L and the company's recalculated baseline being 7.9mmol/L from the Thompson *et al.* imputed baseline of 8.7 mmol/L.

As Thompon *et al.* is likely to overestimate baseline risk compared to those seen in a more contemporary patient population, the EAG conducted a scenario using the Weibull distribution to extrapolated CV mortality in the model. The Weibull was chosen as it resulted in the second lowest Akaike and Bayesian information criterion (AIC and BIC) scores, with the Gompertz used in the base case resulting in the lowest, and provided the next best visual fit. The results of the scenario using the Weibull extrapolation are outlined in **Error! Reference source not found.**. By lowering baseline risk in the model, life years increased across all health technologies with no change in the nature of the ICERs.

Table 10. Scenario analysis extrapolating CV mortality using the Weibull distribution

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Evinacumab vs lomitapide, MAIC excluding lomitapide treated evinacumab patients									
Lomitapide	7,290,597	15.65	12.08	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs lomitapide, MAIC including lomitapide treated evinacumab patients									
Lomitapide	7,172,120	15.39	11.88	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Evinacumab vs LLTs									
LLTs	328,629	14.87	11.47	-	-	-	-	-	-
Evinacumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

3.6 Key issue 6: Baseline LDL-C used in the model

In response to the EAG's key issue, the company stated that the EAG's use of the LDL-C baseline from ELIPSE introduces additional uncertainty compared to the Company's approach as without adjusting the underlying baseline risk from Thompson *et al.* a disconnect is created between

baseline LDL-C used to calculate a treatment effect and baseline risk. The EAG's approach therefore applies the unadjusted CV mortality risk from Thompson *et al.*, which goes on to informs CV event risk in the model.[1]

The EAG agrees with the company and thanks them for identifying this issue. Given the linear relationship assumed in the model between LDL-C reduction and CV risk and, to align the baseline risk from Thompson *et al.* to reflect that of the LDL-C baseline in ELIPSE, the EAG has applied the difference in LDL-C between ELIPSE and Thompson *et al.* to the treatment effects, thereby applying a LDL-C reduction so that baseline risk from Thompson *et al.* reflects LDL-C in the mode.[1] This update to the EAG's preferred assumptions leads to an accentuation of the previous base case ICERs with no change in their location on the cost effectiveness plane (Table 5).

The EAG considers its approach to be more robust and transparent given it utilises the established linear relationship between LDL-C and CV risk. This contrasts with the Company's approach, which requires many assumptions to be made about the comparability of the estimated treatment effects across multiple studies and the appropriateness of combining these disparate estimates of effectives to estimate a baseline efficacy of an assumed bundle of LLTs.

4 Additional issues

In addition to responding to the EAG's key issues, the company has identified additional issues with the EAG report.

4.1 Additional issue 1: incorrect calculation by the EAG of evinacumab usage (vial wastage)

The company has stated that the EAG has incorrectly calculated the number of vials required for treatment with evinacumab due to double counting vial wastage. The company notes that in their calculations, wastage had already been accounted for and so the rounding up by the EAG from 3.65 to 4 vials per administration is inappropriate as wastage is therefore being taken into account twice.

The company's method for calculating the number of vials of evinacumab was to take the mean weight of patients from ELIPSE and fit the data to a log normal distribution. Using the modelled weight distribution and dosing evinacumab at 15mg/kg, the number of vials per patient for evinacumab was calculated by the company at 3.65. Comparatively, in the absence of the observed weight data from ELIPSE, the EAG preferred to use the mean weight reported from ELIPSE to directly calculate the mean number of vials required per administration, resulting in 3.16 vials, rounding to 4 whole vials.

During the TE process the company was able to provide the EAG with the ELIPSE patient weights as detailed in Table 11. Using these data, the EAG calculated the weighted average of the number of vials required for each administration (3.65) which was incorporated into the EAG's base case assumptions (Table 5). The EAG considers 3.65 vials to appropriately include any wastage.

Table 11. ELIPSE patient body weight

Bodyweight category	Number of vials required for each administration	Number of patients	Proportion of patients
(0, 46kg]	2	3	5%
(46kg, 69kg]	3	29	45%
(69kg, 92kg]	4	25	38%
(92kg, 115kg]	5	5	8%
(115kg, 138kg]	6	2	3%
(138kg, 161kg]	7	1	2%
Total		65	100%

Abbreviation: kg, kilo gram.

4.2 Additional issue 2: Apheresis disutility

The company identified an error in the EAG's calculation of apheresis disutility. The EAG thanks the company for highlighting this error. The EAG's base case has been corrected to reflect apheresis disutility as previously calculated by the company (Table 3).

5 References

1. Thompson GR. Managing homozygous familial hypercholesterolaemia from cradle to grave. *Atheroscler Suppl* 2015; **18**: 16-20.
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8. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007; **11**: 1-160, iii-iv.
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Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Addendum

October 2023

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 133488.

1 Introduction

Following the company submitting a model that allowed the running of a probabilistic sensitivity analyse (PSA) using user defined inputs, the EAG (External Assessment Group) provides in this addendum the deterministic and probabilistic results of the company and EAGs base case assumptions and the EAGs scenario evaluating the cost effectiveness of evinacumab in adolescent populations from the EAGs TE response.

2 Company and EAG base case results

Table 1 outlines the company's corrected base case deterministic and probabilistic results. The company's base case assumptions were corrected to the eMIT prices for atorvastatin and ezetimibe and the PSSRU 2022 costs for blood samples and GP appointments.

Table 1. Corrected company TE base case deterministic and probabilistic results

Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Company base case assumptions							
Lomitapide (deterministic)	5,976,577	10.05	-	-	-	-	-
Evinacumab (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lomitapide (probabilistic)	6,041,316	12.98	-	-	-	-	-
Evinacumab (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

Table 2 provides the EAGs deterministic and probabilistic results using the MAIC treatment effects which include or exclude lomitapide treated evinacumab patients from the evinacumab arm of the ELIPSE trial, and considering continuation of LLTs as a comparator to evinacumab.

Table 2. EAG TE updated base case deterministic and probabilistic results

Intervention	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Using MAIC treatment effects excluding lomitapide treated evinacumab patients							
Lomitapide (deterministic)	6,280,861	10.45	-	-	-	-	-
Evinacumab (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lomitapide (probabilistic)	6,230,840	10.37	-	-	-	-	-
Evinacumab probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using MAIC treatment effects including lomitapide treated evinacumab patients							
Lomitapide (deterministic)	6,159,794	10.25	-	-		-	-
Evinacumab (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lomitapide (probabilistic)	6,170,821	10.25	-	-	-	-	-
Evinacumab probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparing evinacumab to the continuation of LLTs							
LLTs (deterministic)	289,607	9.85				-	-
Evinacumab (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LLTs (probabilistic)	291,101	10.09	-	-	-	-	-
Evinacumab (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

3 EAG scenario analysis

The EAG has additionally provided the deterministic and probabilistic results of the EAG scenario comparing evinacumab to lomitapide in the adolescent population (Table 3).

Table 3. EAG evinacumab treatment of adolescent population scenario

Intervention	Total Costs (£)	Total QALYs	inc. costs (£)	inc. QALYs	ICER (£/QALY)	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Using MAIC treatment effects excluding lomitapide treated evinacumab patients							
LLTs & lomitapide (deterministic)	7,601,346	18.3	-	-	-	-	-
Evinacumab (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LLTs & lomitapide (probabilistic)	7,588,644	18.4	-	-	-	-	-
Evinacumab (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using MAIC treatment effects including lomitapide treated evinacumab patients							
LLTs & lomitapide (deterministic)	7,513,079	18.15	-	-	-	-	-
Evinacumab (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LLTs & lomitapide (probabilistic)	7,481,313	18.2	-	-	-	-	-
Evinacumab (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELIPSE treatment effects							
LLTs (deterministic)	446,459	17.81	-	-	-	-	-
Evinacumab (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LLTs (probabilistic)	445,479	17.86	-	-	-	-	-
Evinacumab (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

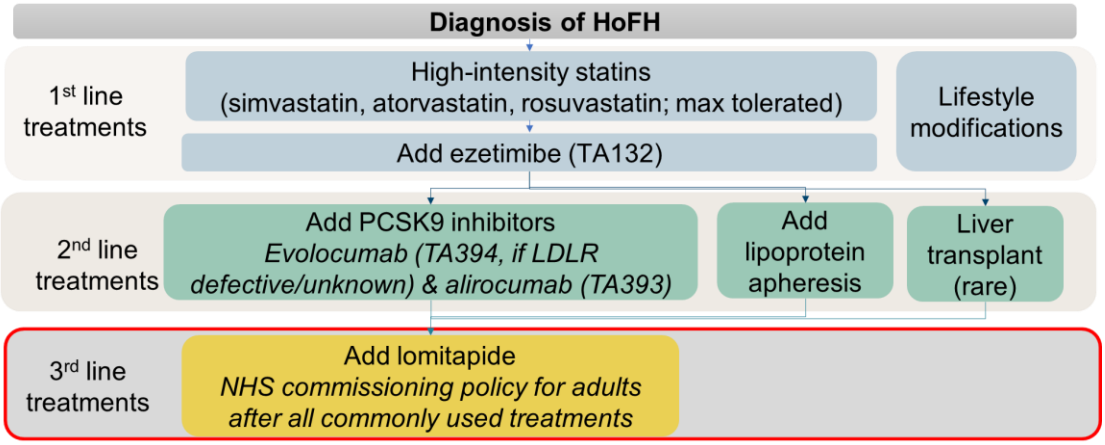
Abbreviations: ICER, incremental cost effectiveness ratio; LLT, lipid lowering therapy, LY, life-year; NHB, net health benefit; QALY, quality adjusted life year; SW, south-west; WTP, willingness to pay.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Queries from NICE technical team to clinical experts on treatment pathway



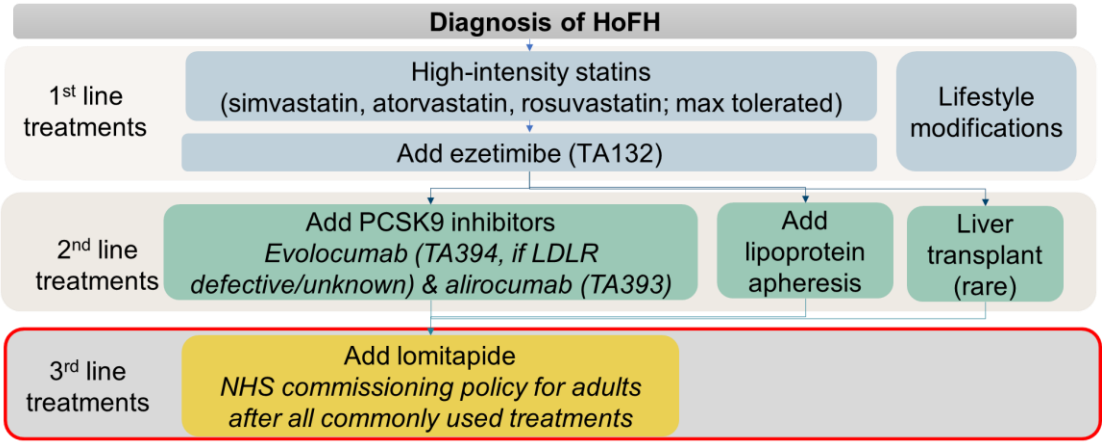
Name	Jaimini Cegla
1. Is the above pathway correct?	
Yes it is. In practice, majority of patients require 1st, 2nd and 3rd line to reach target.	
2. Inclisiran and Bempedoic acid + ezetimibe also have positive NICE recommendations at 2nd line but are not listed in the company or EAG's pathways. Are inclisiran or bempedoic acid + ezetimibe ever used at 2nd line in the NHS?	
Ezetemibe is used extensively in the NHS for homozygous FH. Bempedoic acid much less used as not much extra benefit in combination with high dose statins which most HoFH patients are on. Inclisiran not used in HoFH- preference is PCSK9 mabs which are more potent and have specific higher doses licensed for HoFH. Inclisiran not licensed specifically for HoFH.	
3. Would lipoprotein apheresis ever be used after or in combination with lomitapide?	
Yes we do this in practice frequently	

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 years and over [ID2704]

Queries from NICE technical team to clinical experts on treatment pathway



Name	Handrean Soran

1. Is the above pathway correct?

I attached a pathway from HEART UK's HoFH expert opinion that was also adopted by NHSE when they commissioned Lomitapide. Slide 2 in the attached. I personally believe Evinacumab should be made available for patients as an add on or alternative to apheresis or Lomitapide in patients with no evidence for ASCVD and as an add on in HoFH with evidence of ACVD. Individualizing treatment, patients circumstances and choice should be taken in consideration when we decide which second line to start with. In all patients first line is high intensity statin + Ezetimibe.

2. Inclisiran and Bempedoic acid + ezetimibe also have positive NICE recommendations at 2nd line but are not listed in the company or EAG's pathways. Are inclisiran or bempedoic acid + ezetimibe ever used at 2nd line in the NHS?

- Inclisiran is 1) although the pilot study of 4 patients showed some effect (https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.119.044431?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed), the larger RCT showed inclisiran is ineffective in patients with HoFH

(https://pubmed.ncbi.nlm.nih.gov/37850379/) 2) Commissioned in NHS only for secondary prevention.

- Bempedoic acid is only commissioned in patients who are intolerant for statins. It is a relatively week drug and no clinical trial data in patients with HoFH. We are not sure if it lowers LDL-C at all in patients with HoFH.
- We do not have experience with Bemperdoic acid in HoFH clinically or reseach.
- Taking the above in consideration, there is no point to use inclisiran or bemepedoic acid + ezetimibe ever used at 2nd line
- Ezetimibe is used with statins as the first line unless if there is intolerance or side effects. Hence no point in this second line suggested.

3. Would lipoprotein apheresis ever be used after or in combination with lomitapide?

Yes, in some patients this helps to reach the LDL-C target but in many others apheresis and Lomitapide (maximum tolerated dose) still not enough.

I also like to mention there are many restrictions with both apheresis (availability, distance, taking time off work, vascular access, presence of cardiovascular disease some times means patients may not tolerate this treatment) and lomitapide (side effects, dietary and alcohol restrictions)

HEART UK Consensus Statement – Managing HoFH in the UK

HEART UK
THE CHOLESTEROL CHARITY

HEART UK Statement on the Management of Homozygous Familial Hypercholesterolaemia in the United Kingdom.

Authors/reviewers

Michael France[1], Alan Rees[2], Dev Datta[3], Gilbert Thompson[4], Nigel Capps[5], Gordon Ferns[6] Julian Halcox[7], Uma Ramaswami[8], Mary Seed[9], Dermot Neely[10], Robert Cramb[11], Carol Shoulders[12], Mahmoud Barbir[13], Steven Martin[14], Bill Simpson[15], Ian Young[16], Ray Edwards[17], Steve Boley[18], Linda Main[19], Jules Payne[20], Handrean Soran[21] for HEART UK Medical Scientific and Research Committee.

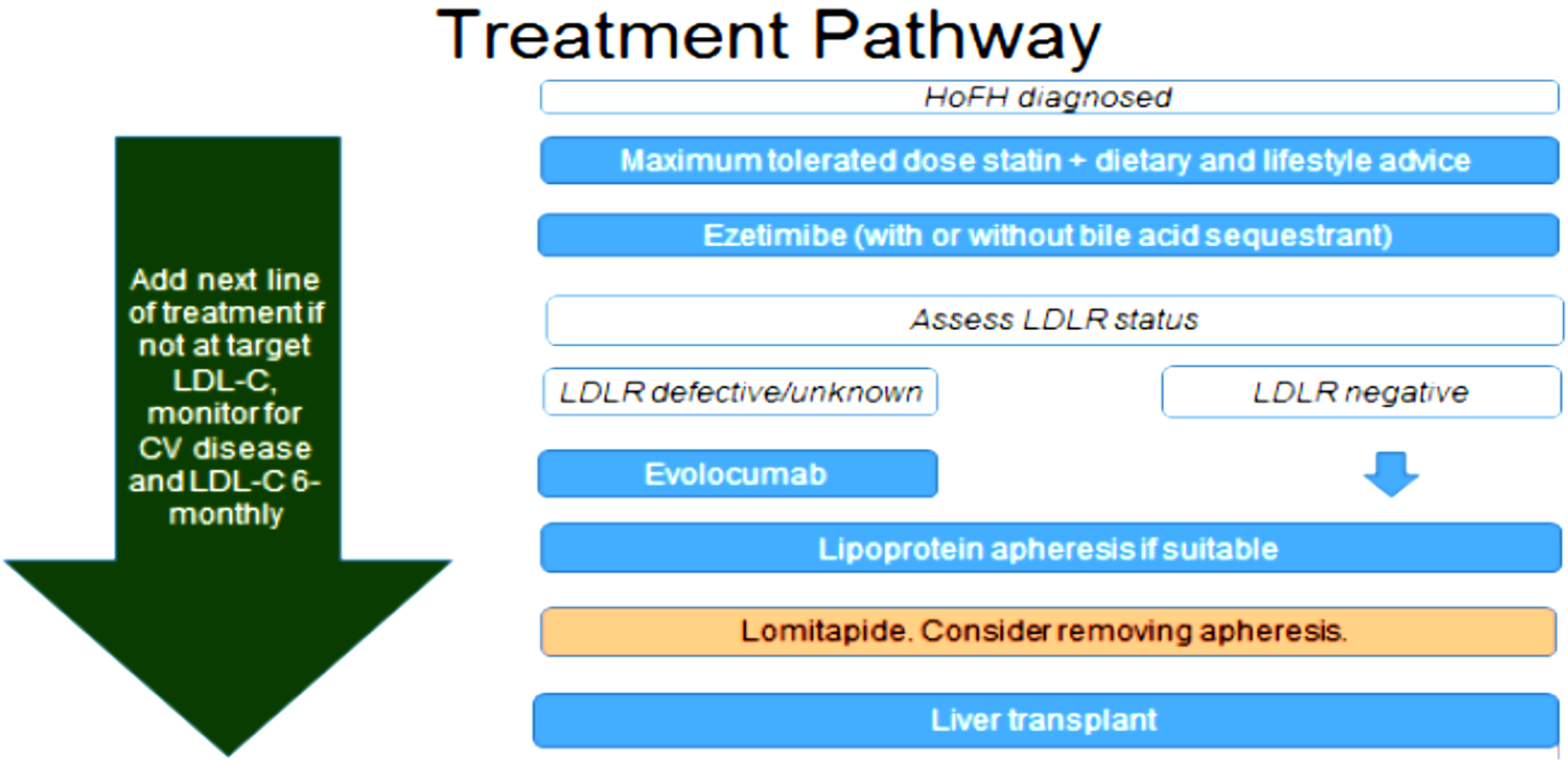
Clinical and genetic criteria for diagnosis of HoFH

Presence of 2 disease causing alleles affecting introns and exons of the LDLR, APOB, PCSK9 and LDLRAP1 gene loci or Total cholesterol >11.0 mmol/L in children with tendon or cutaneous xanthomata before age 10 or 13.0 mmol/L in adults with clinically obvious tendon or cutaneous xanthomata or Qualifying cholesterol level and both parents with genetically confirmed HeFH

Lipoprotein targets (interval mean if on lipoprotein apheresis)	LDL-C mmol/L	Non-HDL-C mmol/L
Adults > 18	< 2.5	< 3.3
Adults with CVD	< 1.8	< 2.6
Children	< 3.5	< 4.3

France M et al. *Atherosclerosis.* 2016; 255: 128-139

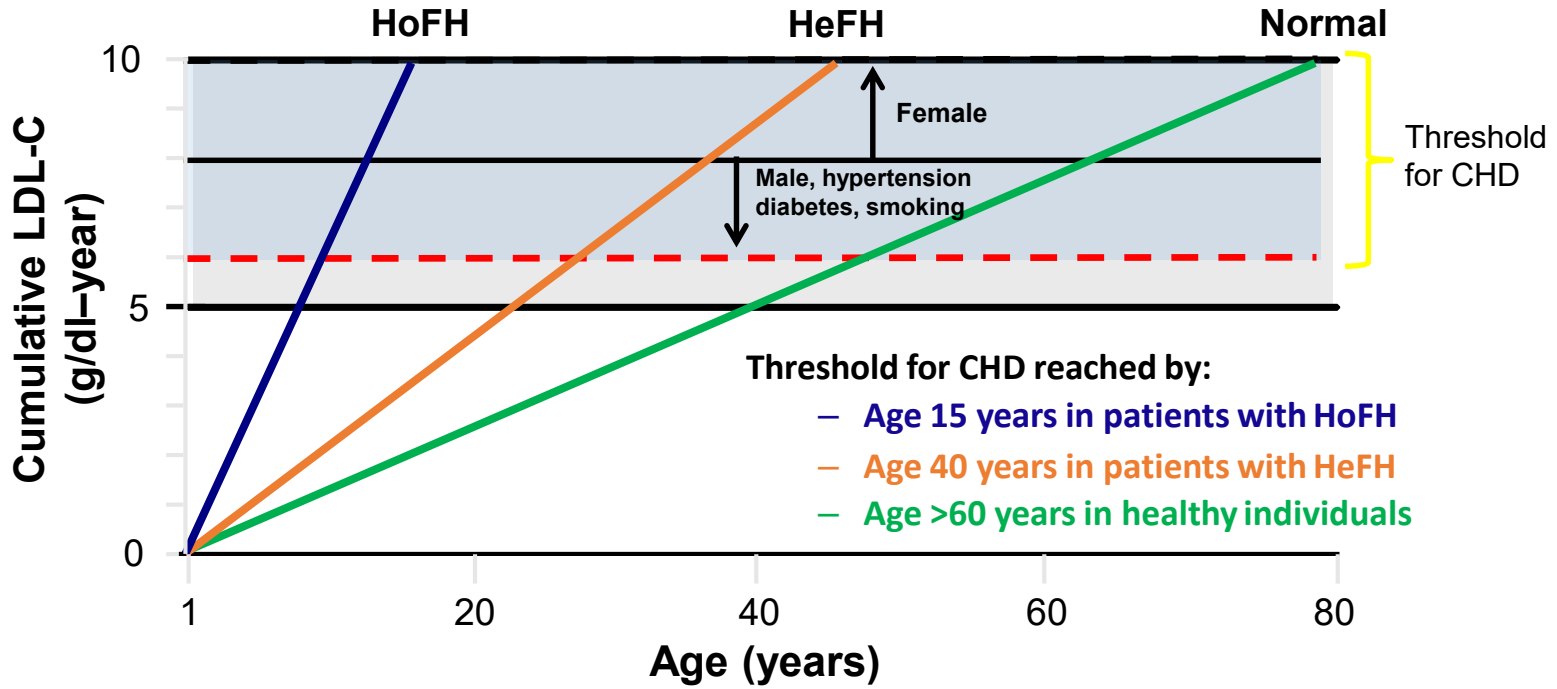
Lomitapide NHS England pathway



NHS England: Clinical Commissioning Policy: Lomitapide for treating HoFH (adults) June 2018

HoFH and CHD Risk

Cumulative exposure (cholesterol-years) by age: patients with FH vs healthy individuals



Threshold for CHD reached by:

- **Age 15 years in patients with HoFH**
- **Age 40 years in patients with HeFH**
- **Age >60 years in healthy individuals**

Adapted from Horton JD *et al*. *J Lipid Res* 2009;50(suppl):S172