Evinacumab for the treatment of homozygous familial hypercholesterolaemia

For committee - CON information redacted [redacted]

Technology appraisal committee C [02 July 2024]

Chair: Stephen O'Brien

External assessment group: BMJ TAG

Technical team: Owen Swales, Sally Doss, Emily Crowe

Company: Ultragenyx

Evinacumab for the treatment of homozygous familial hypercholesterolaemia

- ✓ **Background to the appraisal**
- ❑ Stakeholder engagement responses
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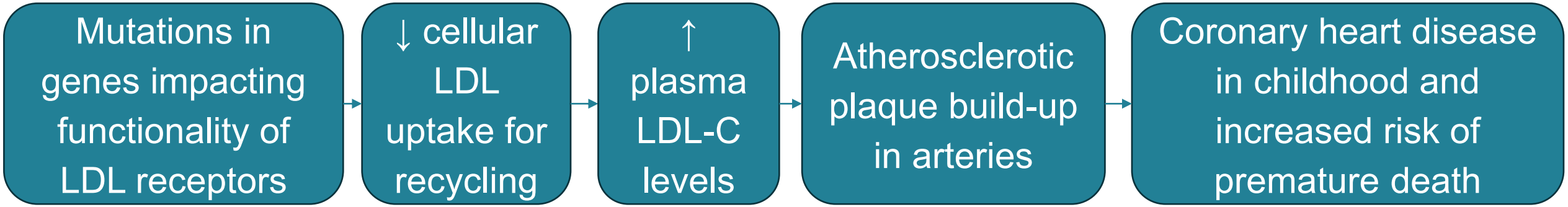
Homozygous familial hypercholesterolaemia

Rare low-density lipoprotein receptor disorder causing early cardiovascular disease



Epidemiology: approx 1: 670,000 adults in England* (total 43 to 66 adults; 1 new case/ year)

Diagnosis: presence of symptoms and family history; confirmed with genetic testing

Classification: spectrum of severity related to mutation: may cause complete or partial loss of LDLR function -> most severe being null/null (almost complete loss of function).

Prognosis: early death common from CV events (MI, stroke, and heart failure)

*Source: lomitapide clinical commissioning policy using Office for National Statistics [ONS] 2016 data. CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MI, myocardial infarction

Technology (EVKEEZA, Ultragenyx)

Marketing authorisation	MHRA approval granted in August 2022 for use *"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)."*
Mechanism of action	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, triglycerides, high density lipoprotein-cholesterol and other lipoproteins
Administration	15 mg/kg administered by intravenous infusion every 4 weeks
Price	• List price per pack: £6,433 per 345 mg vial • List price for 12 months of treatment: £282,472* • A patient access scheme is applicable

MHRA, Medicines and Healthcare products Regulatory Agency. *source: company's budget impact model

Committee recommendation after ACM1

"The committee concluded that **evinacumab was cost saving compared with lomitapide**. Although there were negative QALYs accrued in its preferred analyses, this was uncertain…**agreed that evinacumab was a replacement for lomitapide**"

"The cost-effectiveness analyses **compared with LLTs were above the [cost-effectiveness] threshold**...But the committee considered these **estimates were not appropriate for decision making**. It acknowledged that the population who have LLTs (with or without lipoprotein apheresis) had a **high unmet need** because:

- LLTs have limited effectiveness in people with HoFH
- lipoprotein apheresis can be traumatic and time consuming
- this population includes young people, so there is a potential for an inequality of access by age."

"The committee considered these **exceptional circumstances** that warranted flexibility in its recommendation. So, it **recommended evinacumab** for the whole population"

HoFH, homozygous familial hypercholesterolaemia; LLT, lipid lowering therapy

Appraisal timeline leading up to ACM2

NICE received a non-appeal request for change on the FDG after ACM1

ACM1 – 14 Nov 2023

Positive FDG released

- **Adults:** ICER for evinacumab vs lomitapide is cost effective
- **Ages 12 to 17:** ICER for evinacumab vs LLTs not reliable, recommended due to unmet need and age inequality concerns

Consultation – Dec 2023

Non-appeal request for change from Chiesi

- Lomitapide dose in modelling is higher than in clinical practice
- D'Erasmo (2021) cites lower lomitapide dose (mean: 20 mg)
- Shared confidential lomitapide dose data

ACM2 – 02 July 2024

Asked to reconsider lomitapide dose

Stakeholder engagement responses from:

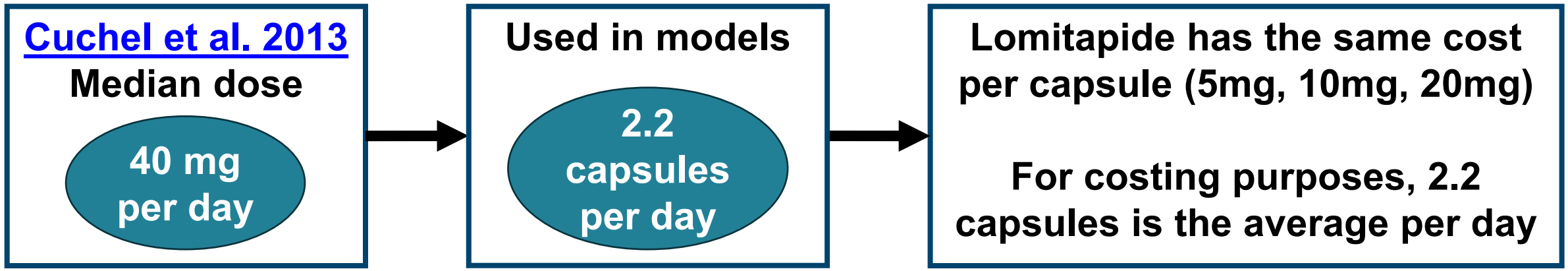
- Ultragenyx (evinacumab)
- Chiesi (lomitapide)
- NHS England
- HEART UK
- Clinical experts

FDG, final draft guidance; LLT, lipid lowering therapy

Lomitapide dose and treatment effect at ACM1

Committee concluded the treatment effect of lomitapide was uncertain

Lomitapide dose used in company and EAG base cases at ACM1



Committee conclusion on lomitapide treatment effect (from withdrawn FDG)

"…although it is plausible that evinacumab will work at least equally as well as lomitapide in clinical practice, the true difference in treatment effect was unknown. It preferred the treatment effect from the MAIC that excluded people having lomitapide in the evinacumab arm of ELIPSE…[the results suggested that lomitapide was more effective than evinacumab]…recalled the uncertainty in the treatment effect of lomitapide vs evinacumab"

FDG, final draft guidance; MAIC, matching adjusted indirect comparison

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Stakeholder engagement responses (1)

Dosing information shared by the companies for evinacumab and lomitapide

Ultragenyx (evinacumab)

- Dosing of lomitapide needs to be dynamic depending on response and tolerability
- Smooth titration to target, including down titration, should involve all doses between 5 mg and 60 mg being made available on a clinical basis according to patient need
- Cuchel et al. 2013 was the only study that reported data comparable to ELIPSE RCT
- Data from the Cuchel study and the intervention arm of ELIPSE used in a MAIC
- Observational studies cannot be used in modelling as they did not adequately report dosage or capsule usage and they cannot be used to reliably link dose with efficacy
- If observational data is used, should be via a cost-minimisation analysis

Chiesi (lomitapide)

- Shared 11 studies and confidential lomitapide dosing data from the LOWER study
- Confidential dosing data shows a lower dose of lomitapide is used in real-world practice
- Studies suggest lomitapide is highly effective at lower doses

MAIC, matching adjusted indirect comparison; RCT, randomised controlled trial

Stakeholder engagement responses (2)

Real-world doses shared by NHS England, HEART UK and clinical experts

NHS England

- Shared lomitapide dosing for 18 people with HoFH from 5 NHS trusts

Average daily dose: 16.9 mg

Range: 5 to 30 mg

NHS trusts: Manchester, Bristol and Weston, Guy's and St Thomas, Nottingham, Imperial College Healthcare

HEART UK

- Coordinated consensus view from 5 key centres
- All patients are on 1 or 2 capsules a day
- Efficacy of lomitapide is not necessarily dose-dependent, LDL-C reduction is 30-70%

Average daily dose: 1.7 capsules

Key centres: Manchester, Bristol, Birmingham, Brompton and Harefield, Imperial College

Clinical experts

- Most patients end up on 20 mg daily doses and higher if tolerated
- Shared data from Imperial College Healthcare NHS Trust included in summary above

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EAG response to engagement comments

Use HEART UK dose and assume equal treatment effect for lomitapide

Daily lomitapide capsules per adult

- NHS England data equates to **1.4 capsules a day**, by assuming capsules per dose
- No studies shared by Chiesi are suitable for inclusion in an MAIC with evinacumab due to poor methods reporting, risks of bias, small samples and generalisability concerns
- 2.2 capsules used in previous model was too high
- EAG prefers HEART UK estimate as it's based on actual capsule usage and not assumed capsule usage

EAG average daily dose

1.7 capsules

Lomitapide treatment effect for adjusted dose

- No robust data to inform a reliable estimate of the treatment effect of lomitapide (alone or versus evinacumab) in NHS clinical practice for the likely dose used in practice
- Main driver of ICERs is cost-based (incremental QALYs is [redacted]), so **assume equal QALYs for evinacumab and lomitapide** via a cost-minimisation analysis

What number of lomitapide capsules should be used in modelling?
What is the relative effectiveness of evinacumab vs lomitapide in clinical practice?
Is it reasonable to assume equal QALYs for evinacumab and lomitapide?

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RECAP

Committee preferred assumptions at ACM1

Lomitapide capsules per dose, relative efficacy and preferred ICER threshold

Number of lomitapide capsules used per dose

- Aligned with company and EAG base cases

2.2 capsules

Relative efficacy of lomitapide

- Plausible that evinacumab will work at least equally as well as lomitapide in practice
- True difference in treatment effect was unknown
- Preferred the MAIC treatment effect that excluded people having lomitapide in the evinacumab arm to minimise uncertainty and align populations → mean LDL-C reduction from baseline was 6% higher for lomitapide (95% CI: -26% to +39%)
- Recalled uncertainty in the treatment effect of lomitapide compared with evinacumab
- Noted that evinacumab was still cost effective when using the EAG's cost-minimisation analysis that assumed an equal treatment effect to lomitapide

HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol

RECAP

Committee considerations for adolescents at ACM1

No reliable ICERs for decision-making but recommended due to unmet need

Background to considerations for adolescents

- Licence includes people aged 12 + and there is a high unmet need in young people
- Company did not present ICERs for young people because of a lack of data
- EAG highlighted this made evinacumab clinical effectiveness extremely uncertain
- Committee was concerned that the benefits of starting evinacumab early on long-term cardiovascular outcomes may not have been captured in the modelling
- Committee noted that there were few young people with HoFH in the NHS

Committee conclusion for adolescents

- Adolescent ICERs > £30k but benefits are uncaptured as model started at age 42
- No reliable cost-effectiveness analyses to use for decision-making
- But, committee recommended evinacumab for adolescents due to exceptional circumstances that warranted flexibility: LLTs have limited effectiveness; lipoprotein apheresis can be traumatic and time consuming; potential for an inequality of access by age if recommended for adults but not young people

HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol

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To be discussed by committee in Part 2

Confidential dosing data for lomitapide and ICERs

Lomitapide dosing data

- Confidential lomitapide dosing data shared by Chiesi

Cost-effectiveness results

- Original company base case
- Original EAG base case
- Updated EAG base case

EAG scenario analysis

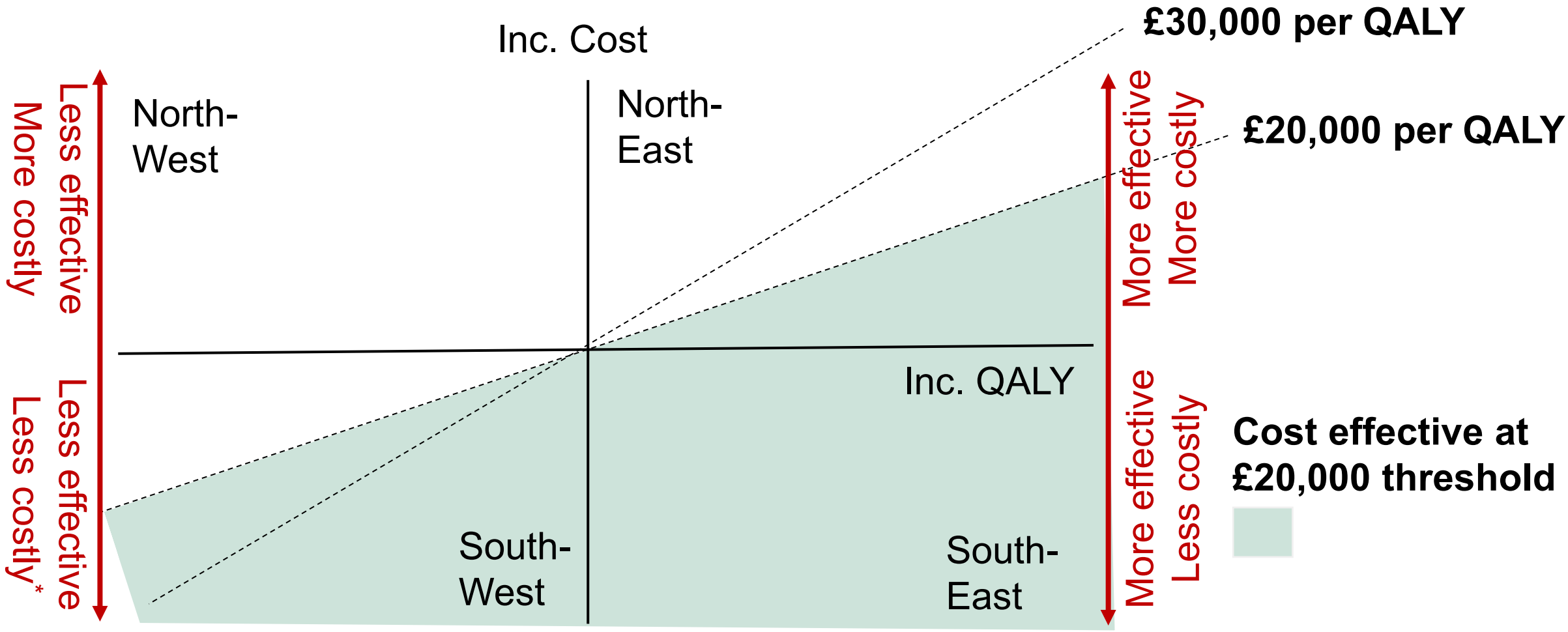
- 1.7 lomitapide capsules – evinacumab cost effective
- 2.0 lomitapide capsules – evinacumab cost effective
- 1.0 lomitapide capsules – evinacumab not cost effective
- Lomitapide capsule threshold analysis
- 1.7 lomitapide capsules per dose and lomitapide efficacy equal to evinacumab **(EAG preferred analysis)** – evinacumab cost saving

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

PAS, patient access scheme

The cost-effectiveness plane

Some ICERs are not in the typical North-East quadrant



QALY, quality adjusted life year. *Higher ICERs are most cost-effective in the SW quadrant

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Thank you

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Supplementary appendix

Cuchel et al. 2013

Summary of the Cuchel et al. 2013 study

	Cuchel et al. 2013
Design	Phase 3, single-arm, open-label study
Population	People with HoFH (N = 29)
Intervention	Lomitapide
Comparator	N/A – single-arm
Duration	Efficacy phase to Week 26; Safety assessed to Week 78
Primary outcome	Mean percent change from baseline in LDL-C at week 26
Key secondary outcomes	Percent changes in other lipid parameters, long-term safety and changes in hepatic fat content
Locations	USA, Canada, South Africa and Italy

HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol

ELIPSE trial

	ELIPSE
Design	Phase 3, double blind RCT
Population	People ≥12 years with HoFH
Evinacumab	15 mg/kg IV Q4W
Comparator	Placebo
Duration	24 weeks RCT + 24 weeks open label treatment
1° outcome	% change in calculated LDL-C from baseline to week 24
Key 2° outcomes (assessed at 24 weeks)	% change in other lipid parameters (Apo B, non-HDL-C, and TC); % with ≥30% and ≥50% reduction in LDL-C; % with LDL-C of <100 mg/dL (2.59 mmol/L) and <70 mg/dL (1.81 mmol/L); % meeting apheresis eligibility criteria; PK; antibody status; TEAEs and HRQoL
Locations	Global (including Europe). No UK sites.
In model?	Yes

ApoB, Apolipoprotein B; HDL, high-density lipoprotein; HRQoL, health-related quality of life; IV, intravenous; LDL-C, Low-density lipoprotein cholesterol; RCT, randomised controlled trial; PK, pharmacokinetic; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event; TC, total cholesterol

NHS England lomitapide dosing data and EAG estimations

Summary of NHS England lomitapide dosing data

Lomitapide dose daily	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg	40 mg	60 mg
Number of patients	3	3	3	5	1	3	0	0
Proportion (%)	16.7	16.7	16.7	27.8	5.6	16.7	0.0	0.0
Average dose = 16.94 mg								

EAG assumed number of capsules required per dose of lomitapide

	Number of capsules required per dose of lomitapide (assumed)					
Dose	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Capsules required	1	1	2	1	2	2

= 1.4 capsules per day