For public - redacted

Evinacumab for the treatment of homozygous familial hypercholesterolaemia ID2704

Technology appraisal committee C 14th November 2023

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Company: Ultragenyx

Evinacumab for the treatment of homozygous familial hypercholesterolaemia

- ✓ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Link to supplementary appendix: clinical trials (1) and (2), pivotal trial design, baseline characteristics, adverse events and secondary endpoints

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 345mg 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

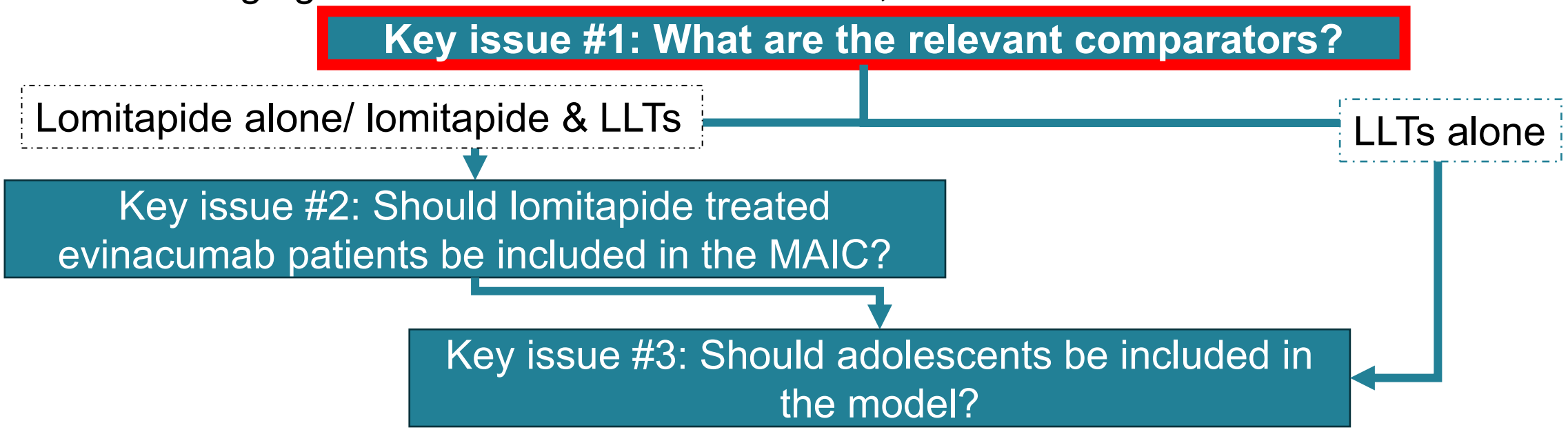
Key issues

Issue	Resolved?
Decision changing ICERs: for discussion in ACM1, Part 1	
Main key issue: What are the comparators for evinacumab? Lomitapide alone, LLTs alone or both?	No – for discussion
Should lomitapide treated evinacumab patients be excluded from the MAIC?	No – may be discussed depending on issue #1
Should adolescents be included in the analysis?	No – for discussion
Issues with non-decision changing ICERs (see supplementary appendix slides)	
Is it appropriate to assume 100% have no prior CV event history (1° prevention)?	No (slides 44, 45 & 46)
Is CV mortality overestimated?	No (slides 47 & 21)
Is baseline LDL-C overestimated?	No (slides 48 & 49)
How many vials used for an evinacumab administration?	Yes

CV, cardiovascular; LDL, Low-density lipoprotein cholesterol cholesterol ; ICER; incremental cost effectiveness ratio; LLT, lipid lowering therapy; MAIC, matching-adjusted indirect comparison

Key issues

Decision changing ICERs: for discussion in ACM1, Part 1

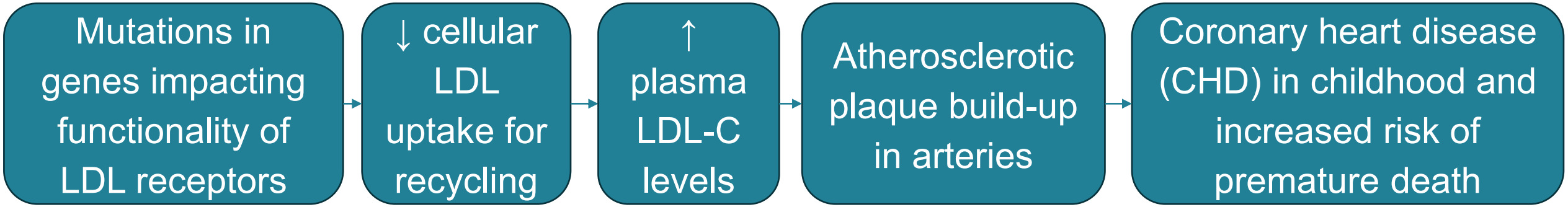


Issues with non-decision changing ICERs (see appendix slides)	Resolved?
100% have no prior CV event history (1° prevention)	No (slides 44, 45, 46)
CV mortality may be overestimated	No (slides 47, 21)
Baseline LDL-C may be overestimated	No (slides 48, 49)
Vial usage (3.6 or 4 vials per administration)	Yes

CV, cardiovascular; LDL-C, Low-density lipoprotein cholesterol; ICER; incremental cost effectiveness ratio; LLT, lipid lowering therapy; MAIC, matching-adjusted indirect comparison

Background on homozygous familial hypercholesterolaemia

Rare low-density lipoprotein receptor (LDLR) disorder causing early cardiovascular disease



Epidemiology: estimated 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

Link to supplementary appendix: decision problem

Patient and clinical perspectives

Submissions from HEART UK – The Cholesterol Charity and patient experts at TE

Current treatment pathway

- Misdiagnosis common: can take years for diagnosis
- Unmet need for new treatments: current options don't reduce LDL-C to target levels
  - ❖ LDL apheresis challenging: time consuming, limited UK locations, venous access
  - ❖ Lomitapide effective but has gastric side effects
- Aim: reduce onset & progression of CV disease, aortic root and cardiac valve disease
- Evinacumab likely given in 3° centres where patients receive other HoFH treatment: potential for home administration

Benefits of evinacumab

- <40 UK HoFH patients likely need evinacumab in clinical practice
- Easy administration (1hr infusion Q4W), effective & well tolerated in trials
- May allow reduction of statin dose and need for or regularity of LDL apheresis

CV, cardiovascular; LDL-C, Low-density lipoprotein cholesterol ; Q4W, every 4 weeks; TE, technical engagement

Link to supplementary appendix: further patient and clinical perspectives

NICE pathway for HoFH

Additional treatments added to 1st line statins +/- apheresis; evinacumab positioned at 3rd line

Diagnosis of HoFH

1st line treatments

- High-intensity statins (simvastatin, atorvastatin, rosuvastatin; max tolerated)
- Add ezetimibe (TA132)
- Lifestyle modifications

2nd line treatments

- Add PCSK9 inhibitors *Evolocumab (TA394, if LDLR defective/unknown) or alirocumab (TA393)*
- Add LDL apheresis
- Liver transplant (rare)

3rd line treatments

- Add lomitapide *NHS commissioning policy for adults after all commonly used treatments*
- ***Company's positioning of evinacumab (added to 1st and 2nd line LLTs)***

- Is the above pathway correct? Is the positioning of evinacumab correct?
- Are inclisiran (TA733) or bempedoic acid + ezetimibe (TA694) used at 2nd line in the NHS?
- Would apheresis ever be used after or in combination with lomitapide?

TA, technology appraisal; LDLR, Low-density lipoprotein receptor; LLT, lipid lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9

Key issue #1: Comparators (1)

EAG: LLTs relevant comparator in adolescents + people who cannot have lomitapide

Background: Lomitapide is company's only comparator: evinacumab will directly replace it

- Lomitapide is only licenced in adults but adolescents (≥12 years) in MA for evinacumab:
  - ❖ No company comparator in adolescent population
- Lomitapide has an NHS commissioning policy: no NICE TA vs LLTs
- Lomitapide requires a low-fat diet (≤20% from fat) before & during treatment.

EAG: LLTs relevant comparator in people who cannot have lomitapide:

- ❖ Lomitapide associated with toxicities: if cannot use it, people continue LLTs
- LLTs main comparator in adolescent patients (*see key issue #3*)
- LDL apheresis potential comparator? Lomitapide positioned after apheresis in NHS commissioning policy, but at same or later lines as apheresis in EAS guidelines

Clinical expert: ~50% stop lomitapide due to toxicity: no other treatment option

- Further therapy always used adjunctively to background LLTs
- LDL apheresis and evinacumab may be used concurrently: apheresis + lomitapide used to help reach LDL-C target in some people -> may still not be enough
- Use evinacumab in high-risk patients, especially if apheresis +/- lomitapide unsuccessful

EAS, European Atherosclerosis Society; LDL-C, Low-density lipoprotein cholesterol; LLTs, lipid lowering therapies; MA, marketing authorisation, TA, technology appraisal

Key issue #1: Comparators (2)

Company: lomitapide only relevant comparator, evinacumab will directly replace it

Company (response to TE):

Lomitapide: only relevant comparator

- Lomitapide toxicities occur during treatment: few people contraindicated at initiation
  - Evinacumab is a direct replacement for lomitapide so same populations at initiation

Background LLTs: not relevant comparator

- Same treatment pathway in adolescents & adults except for lomitapide

LDL apheresis: Base case follows EAS 2014 pathway which assumes prior LDL apheresis

- ***Scenario:*** LDL apheresis used after lomitapide/ evinacumab

NHS England commissioning policy - Lomitapide used when HoFH:

- ***is not adequately controlled by existing treatments (statins, ezetimibe, bowel assisted sequestrants, evolocumab, apheresis) AND***
- ***at high risk of CV events defined as LDL-C:***
  - ***>2.5mmol/L with FH***
  - ***>1.8mmol/L with atherosclerotic CV disease***

- Would evinacumab be used after lomitapide?
- Is apheresis a relevant comparator for evinacumab?
- Would the same LDL-C threshold apply to evinacumab (>2.5mmol/L or >1.8mmol/L with atherosclerotic CVD)?

CV, cardiovascular; EAS, European Atherosclerosis Society; FH, familial hypercholesterolaemia; LDL-C, Low-density lipoprotein cholesterol ; LLTs, lipid lowering therapies; TE, technical engagement

Key issue #1: Comparators (3)

Link to key issue #3: population

Eligible population for evinacumab in people currently having LLTs alone unclear

- Homozygous form of FH very rare: small patient numbers under discussion
- NHS commissioning policy for lomitapide: max 66 people have HoFH in UK
- Some have LDL-C controlled on LLTs only, so eligible population for evinacumab consists of:

People currently having lomitapide*	People currently having LLTs
• N=14 LDLR -ve (don't respond to PCSK-9 inhibitors) • N=15 don't respond to initial PCSK-9 inhibitor (LLTs) • N=18 initially respond but don't meet LDL-C target • Eligible = 47 ❖ 28%† can't / won't have low-fat diet & avoid alcohol or have co-morbidities with liver toxicity concerns	• N=13 people who are eligible for lomitapide but can't / won't have it • Unknown number of adolescents
On treatment: 34 (52% of total HoFH patients)	**Minimum on treatment: 13 (20%)**

- What are the relevant comparators for evinacumab? Lomitapide only, LLTs only or both?
- How large is the adolescent population who would be eligible to have evinacumab?
- Have any populations in whom evinacumab would be used in the NHS been missed? E.g. people whose LDL-C is not controlled on lomitapide +/- apheresis?
- Should people who stop lomitapide for toxicity be considered in this table?

*based on NHS commissioning policy for lomitapide. †based on LOWER registry. FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein-cholesterol; LDLR, low-density lipoprotein receptor; LLT, lipid lowering therapy; PCSK9, Proprotein convertase subtilisin/kexin type 9

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Clinical trial results: change in LDL-C (1° outcome)

Reduced LDL-C at week 24 vs placebo and OLE results suggest this is maintained over time.

ELIPSE	Evinacumab		Placebo*		Difference (95% CI)
	n	Result	n	Result	
LS mean % Δ in LDL-C to week 24	43	-47.1%	21	1.9%	**-49.0%** (-65 to -33); p<0.001
LS mean % Δ in LDL-C to week 48	[redacted]	[redacted]	[redacted]	[redacted]	-

R1500-CL-1719 (OLE) †	Evinacumab	
	n	Result (SD)
Mean % Δ in LDL-C to week 24	[redacted]	[redacted]% ([redacted])
Mean % Δ in LDL-C to week 120	[redacted]	[redacted]% ([redacted])

ELIPSE subgroup analyses (mean Δ to week 24)

Adolescents	*Mutation status*	*Background LLT*
Only N=2 <18 years old: results suggest [redacted] to full cohort	About -50% LDL-C reduction for all phenotypes. ❖ Null/null & negative/negative have higher baseline levels	Effect on LDL-C maintained regardless of background therapy

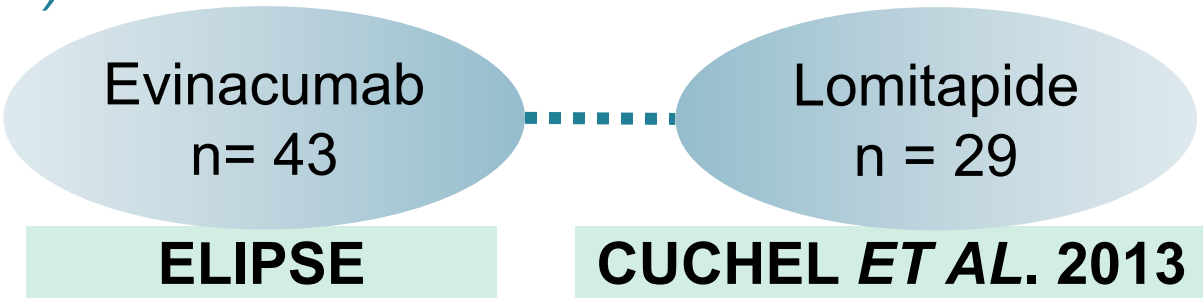
Bold = 1° endpoint. *People randomised to placebo switched to evinacumab from week 24. †Also includes people from R1500-CL-1331 and evinacumab naive. CI, confidence interval; LDL-C, Low-density lipoprotein cholesterol ; LLT, lipid lowering therapy; n, number; OLE, open label extension; SD, standard deviation. Red: used in the company model

Evinacumab vs. lomitapide: indirect treatment comparison

No direct trial data: company use unanchored matching-adjusted indirect comparison (MAIC)

Skip if lomitapide not a comparator

Outcome:
% Δ in LDL-C from baseline



Cuchel *et al.* 2013

- Single arm lomitapide
- 56 week follow up + OLE (max 294 weeks)
- N=6 (21%) discontinued, N=4 due to AEs

Results of the company MAIC for LDL-C, evinacumab vs. lomitapide

Method	Evinacumab n/ESS†	Difference in mean % Δ LDL-C (95% CI)*
MAIC including full ELIPSE population		
Matching age, CHD, LDL-C	9.9	**-15.0% (-36.8 to 6.8)**
Matching age only	23.6	**-16.3% (-30.7 to -1.9)**
MAIC excluding lomitapide treated evinacumab patients in ELIPSE (n=11, 26%)		
Matching age, CHD, LDL-C	3.9	**+6.3% (-26.1 to 38.6)**
Matching age only	16.7	**-14.8% (-30.1 to 0.4)**

*-ve values favour evinacumab, +ve favour lomitapide. † vs 29 lomitapide patients. Company adjusted for prognostic factors only due to limited sample size. AE, adverse event; CHD, coronary heart disease; CI, confidence interval; ESS, effective sample size; LDL, Low-density lipoprotein cholesterol; MAIC, matching-adjusted indirect comparison; n, number; OLE, open label extension

Key issue #2: Reliability of the MAIC (1)

26% on background lomitapide in evinacumab arm of ELIPSE

Background: 26% (n=11) in evinacumab arm of ELIPSE had lomitapide as background therapy

- When excluding these people from the MAIC, results favour lomitapide and effective sample size decreases from 9.9 to 3.9 with wide CIs

Company: excluding lomitapide treated evinacumab patients is inappropriate:

- Different mechanisms of action: no synergy/ antagonism when combined
- Evinacumab has PK profile independent of lomitapide
- Evinacumab efficacy unaffected by lomitapide in ELIPSE subgroup analyses
- Similar TAs accepted concomitant use of additive LLTs
- All published and unpublished data supports ≥ efficacy with lomitapide

Head-to-head trials with lomitapide unlikely for methodological reasons: key uncertainty relates to lomitapide not evinacumab

CI, confidence interval; LLT, lipid-lowering therapy; MAIC, matching adjusted indirect comparison; n, number; PK, pharmacokinetic; TA, technology appraisal

Key issue #2: Reliability of the MAIC (2)

EAG prefer to exclude lomitapide treated evinacumab patients from MAIC

EAG comments: MAIC results uncertain:

- Poor matching: limited baseline characteristic reporting in Cuchel *et al*, small N in trials
- Lomitapide treated evinacumab patients = confounder?
  - ❖ Fully matched cohort without lomitapide treated evinacumab patients most relevant for company's positioning
  - ❖ acknowledge uncertainty in small ESS
- Evinacumab efficacy [redacted] depending on MAIC with wide 95% CIs
- Could interpret MAIC as no substantial difference between treatments.
  - ***Scenario***: cost minimisation analysis
- Likely unresolvable with current evidence

Varying efficacy inputs in key analyses

Evinacumab	Lomitapide	Preferred
MAIC full ELIPSE population: -55.1%	MAIC full ELIPSE population: -40.1%	**Company base case**
ELIPSE: -47.1%	MAIC, no lomitapide treated evinacumab patients: -53.4%*	**EAG base case**
Equal efficacy (cost minimisation)		EAG scenario

- Which efficacy inputs are most plausible?
- Should lomitapide treated evinacumab patients be included in the MAIC?
- Would evinacumab & lomitapide ever be used together?

CI, confidence interval; ESS, effective sample size; MAIC, matching adjusted indirect comparison. *EAG applied Δ between treatments from MAIC to efficacy from ELIPSE

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Link to supplementary appendix:
Model structure and model inputs

Key issue #3: Population (1)

Company does not submit analyses in adolescents despite their inclusion in evinacumab's MA

Background: Adolescents (≥12 years) in MA: company only presents analyses in adults

- Model starting age in company and EAG base cases = 42 years.
- HoFH is a rare disease: N of adolescents eligible for evinacumab unknown (see slide 11)

Company: analyses not presented in adolescents because:

1. Lack of clinical data: only 2 adolescents in ELIPSE and [redacted] in R1500-CL-1719
2. Model not designed for patients at extreme of ages:
   - e.g. Ward et al. for proportion of CV events had lower bound of 40 years: some data cannot be extrapolated to children
3. Adolescent population small: max 5 patients per year

Clinical expert: Vast majority diagnosed <18 years as have florid clinical signs. Occasionally only diagnosed after a cardiac event.

- LDL-C levels rise in adolescence: important to treat this population

CV, cardiovascular; LDL-C, Low-density lipoprotein-cholesterol; MA, marketing authorisation; N, number

Key issue #3: Population (2)

EAG: provides scenarios where people enter model aged 12 to align with full MA population

EAG comments: Clinical and cost-effectiveness in adolescents uncertain:

- model reflects full ELIPSE cohort: few children in trial -> model results generalisable?
- Subgroup analyses suggest [redacted]. Analyses in adolescents [redacted] & appropriately adjusted baseline characteristics & inputs.
- Clinical experts: no difference in treatment effect expected for adults and children
- Final OLE results in adolescent cohort useful for long-term effect

Base case: starting age of 42

Scenarios: starting age of 12 -> large impact on ICER

❖ Likely overestimates non-fatal CV event rates: data from ≥40-year-olds

EAG scenarios with model starting age of 12 years

Comparator	Efficacy input
LLTs until age 18, then lomitapide	ELIPSE treatment effects to age 18 then MAIC effects (with and without lomitapide treated evinacumab patients)
LLTs only (intolerant to lomitapide)	ELIPSE treatment effects

LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; MAIC, matching-adjusted indirect comparison; OLE, open label extension

Should cost-effectiveness analyses in adolescents against LLTs be considered for decision making?

Other key assumptions raised by the EAG

Company base case	EAG comment
CV event history None: 100% 1º prevention patients	- By 42 (model starting age) most HoFH patients have prior CV events - Company: same costs & utilities for 1st and subsequent CV events: evidence suggests implausible **Base case:** 30% 1º prevention, 70% 2º prevention **Scenario:** 100% 2º prevention; adjusted utilities for subsequent events
Baseline LDL-C Individual LLT efficacy applied to difference in use over studies	- Model overestimates baseline LDL-C + reduction in LDL-C vs ELIPSE - Can't directly apply ELIPSE Δ in LDL-C as not linked to CVM source **Base case:** Difference in LDL-C between ELIPSE and Thompson *et al.* applied to treatment effects
CV mortality CVM from Thompson *et al.* extrapolated using Gompertz	Thompson *et al.* includes people having worse treatment than currently offered for HoFH: overestimates CVM **Scenario:** CVM using Weibull (2nd best fit, ↓ CVM risk)

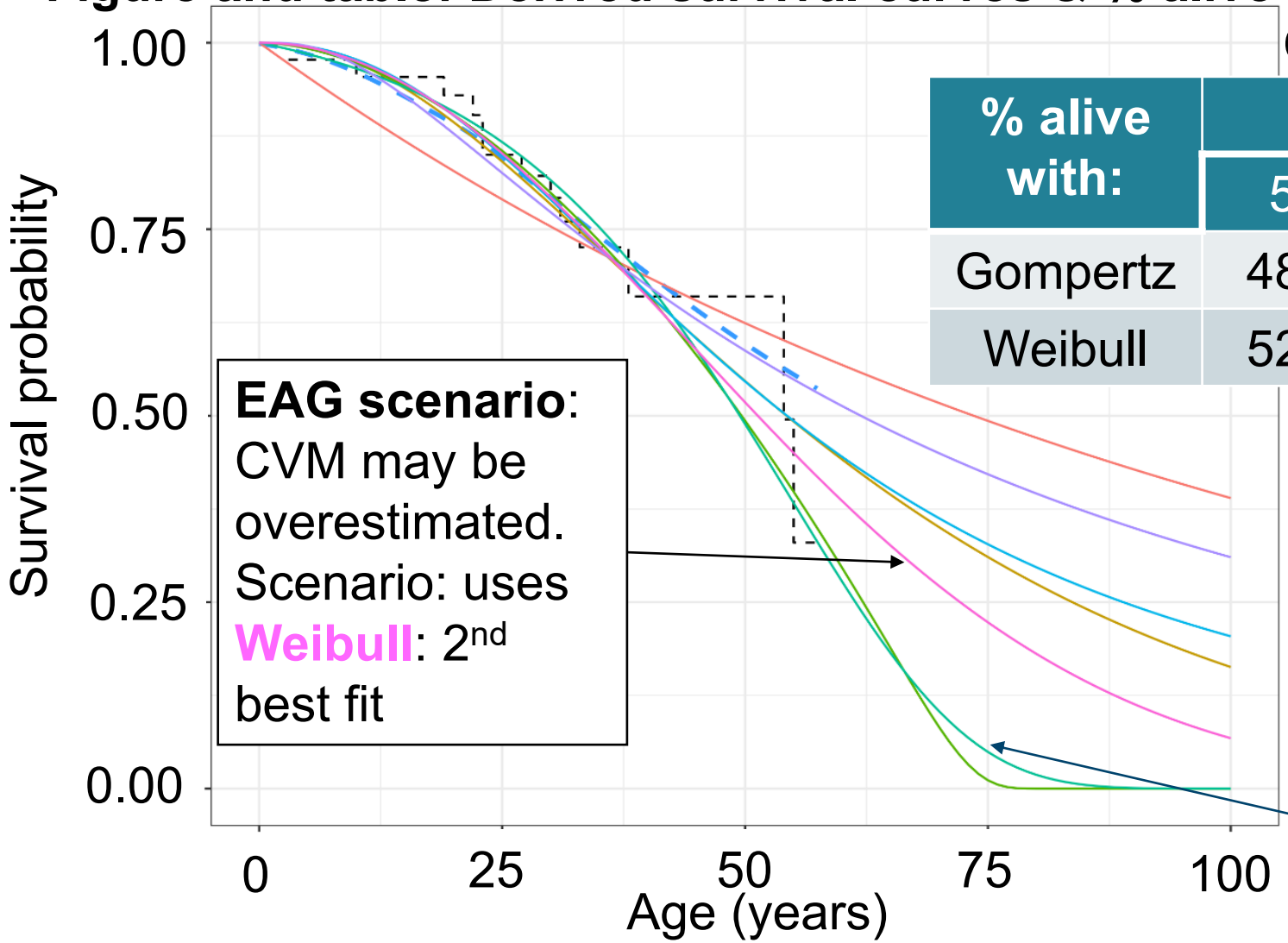
- What % of HoFH patients have had prior CV events by age 42?
- How should baseline LDL-C be modelled?

CV, cardiovascular; CVM, cardiovascular mortality; LDL-C, Low-density lipoprotein cholesterol

Key issue #5: Cardiovascular mortality (CVM)

Company and EAG base cases use Gompertz; EAG scenario uses Weibull

Figure and table: Derived survival curves & % alive at different timepoints based on CVM risks from Thompson *et al.*



% alive with:	Age (years)				
	50	65	70	85	100
Gompertz	48%	18%	10%	1%	0%
Weibull	52%	33%	27%	14%	1%

EAG scenario: CVM may be overestimated. Scenario: uses **Weibull**: 2nd best fit

Exponential
Gamma
Gen-Gamma
Gompertz
Log-logistic
Log-normal
Weibull

Company & EAG use **Gompertz**: lowest AIC/BIC and best fit on visual inspection

Which extrapolation is more plausible, Gompertz or Weibull?

CVM, cardiovascular mortality; AIC, Akaike information criterion; BIC, Bayesian information criterion

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Other considerations

Equalities: Following inequalities should be considered:

- Potential postcode lottery: travel costs, distance to treatment centre will vary by location
- Those who don't meet LDL-C threshold, but HoFH impacts QoL can't access treatment

  NB: The SmPC for evinacumab states only that "before treatment initiation of evinacumab the patient should be on optimal LDL-C lowering regimen"

  - ❖ *NHS clinical commissioning policy for lomitapide: LDL-C of >2.5mmol/L for adults with FH or >1.8mmol/L with atherosclerotic CV disease*
- Evinacumab licenced in people 12 years and over (in whom LLTs are the only comparator)
  - ❖ Inequality of access by age?

Innovation: rare indication with unmet need, first-in-class drug (angiopoietin-like protein 3 (ANGPTL3) inhibitor)

Severity: no case made for applying a severity weighting

LDL-C, Low-density lipoprotein-cholesterol; LLT, lipid lowering therapy; QoL, quality of life; SmPC, summary of product characteristics

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Key assumptions differing in company & EAG base cases

Large impact on the ICER when varying any key issue assumption

Assumption	Company base case	EAG base case	Impact
Comparators	Lomitapide only	Lomitapide, background LLTs	
Treatment effect	MAIC with lomitapide treated evinacumab patients	Lomitapide: MAIC without lomitapide treated evinacumab patients LLTs: ELIPSE	
% 2° prevention	0	70	
Baseline LDL-C	Difference in individual LLT use ELIPSE vs. Thompson *et al.* with individual efficacy's applied for each background LLT	Difference in LDL-C between ELIPSE and Thompson *et al.* applied to treatment effects	

 Decision-changing: changes whether base case is cost effective

 Large impact: >£10,000 per QALY gain change from base case

MAIC, matching adjusted indirect treatment comparison; LDL-C, Low-density lipoprotein cholesterol; LLT, lipid lowering therapy

Supplementary appendix: other differing assumptions in company and EAG base cases

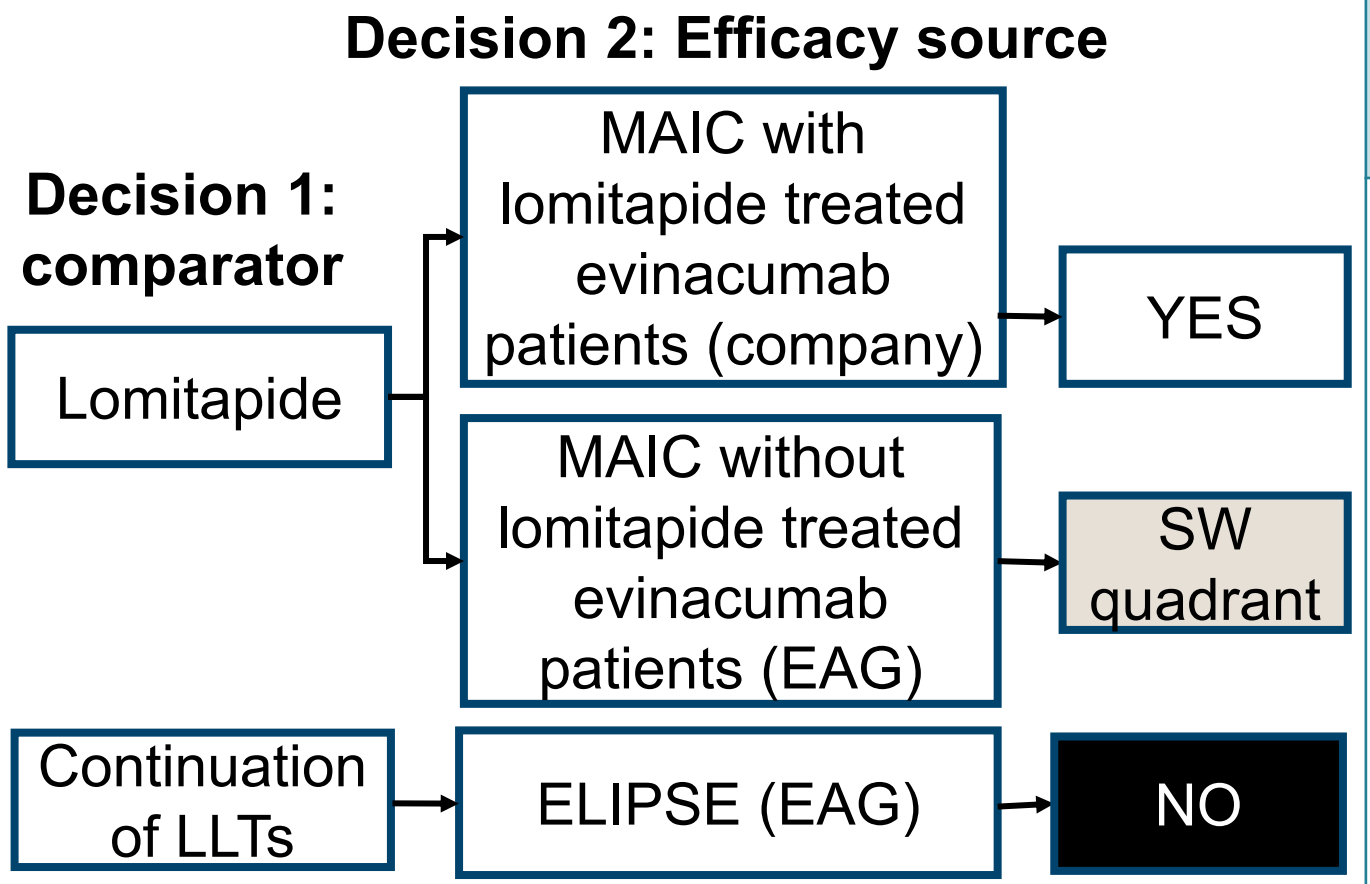
Cost-effectiveness results

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

Key cost-effectiveness scenarios

Link to supplementary appendix: key EAG scenarios

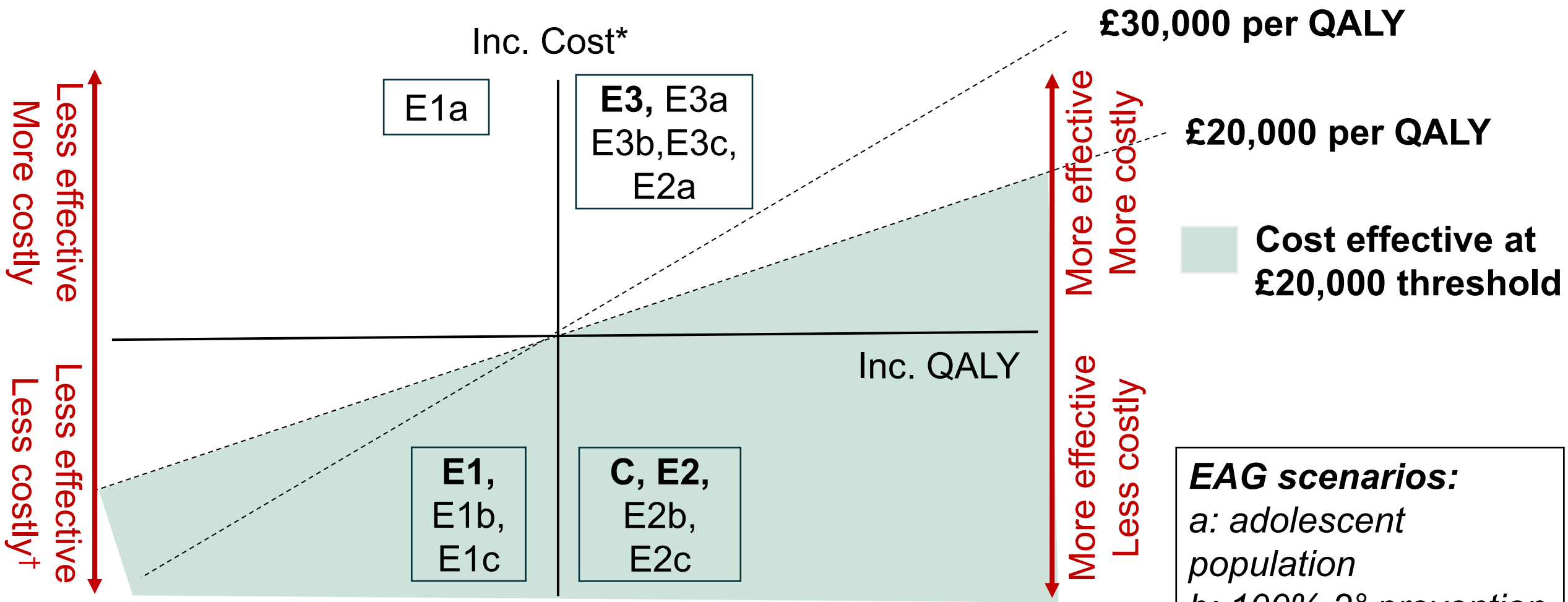
Comparator, efficacy source & including adolescents only decision-changing assumptions



		Cost effective when include:	
		Adolescents?	Weibull for CVM? 2° prevention patients? EAG's baseline LDL-C?
NHB (£30,000 WTP)	+ve vs. lomitapide, -ve vs. LLTs	-ve vs. both comparators	+ve vs. lomitapide, -ve vs. LLTs

CVM, cardiovascular mortality; LDL-C, Low-density lipoprotein-cholesterol; LLT, lipid lowering therapy; MAIC, matching adjusted indirect treatment comparison; NE, northeast; SW, southwest

Key scenarios on the cost-effectiveness plane



EAG scenarios:
a: adolescent population
b: 100% 2° prevention patients
c: using Weibull

EAG base cases:

E1: MAIC excluding lomitapide treated evinacumab patients

E2: MAIC including lomitapide treated evinacumab patients

E3: vs. LLTs

C: Company base case

Inc., incremental; LLT, lipid lowering therapy; MAIC, matching adjusted indirect treatment comparison; QALY, quality adjusted life year. *Placement of box within a quadrant not representative of ICER size † Higher ICERs are most cost-effective in the SW quadrant

Decision making framework

Committee's preferred assumptions?	Question	Answer
Comparators	Comparison with LLTs alone?	
Treatment effect for lomitapide	MAIC with or without lomitapide treated evinacumab patients?	
Population	Analyses from 12 years old (LLTs + lomitapide & LLTs alone) preferred?	
% 2° prevention patients	0%, 50%, 70% or 100%?	
Baseline LDL-C	Company or EAGs approach?	
CV mortality	Using Gompertz or Weibull?	
What is the committee's preferred ICER threshold?		

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MAIC, matching adjusted indirect treatment comparison; LLT, lipid lowering therapy, TA, technology appraisal

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Thank you.

Evinacumab for the treatment of homozygous familial hypercholesterolaemia

Supplementary appendix

NICE

Patient perspectives

Submissions from HEART UK – The Cholesterol Charity and patient experts at TE

Current treatment pathway

- Misdiagnosis common: can take many years for diagnosis
- Access to treatment challenging due to LDL criteria/ funding
  - ❖ Consistent & holistic approach to eligibility criteria essential
  - ❖ Should consider rarity of condition and daily challenges (food, medication, liver conditions)
- Transition from paediatric to adult care problematic
- Apheresis time consuming: weekly travel, doctor's appointments
- Lomitapide effective but associated with gastric side effects
- Diet also challenging to maintain with everyday life

I started plasma exchange treatment at age 11 and lipoprotein apheresis at 13.

I had to see two consultants, a lipidologist and a renal consultant each week before the [apheresis] treatment.

The side effects of Lomitapide are not good and also the long-term effects on the gut health are worrying.

Benefits of evinacumab

- May allow reduction of statin dose: minimise side effects and liver toxicity, especially with early treatment
- Could reduce need for or regularity of apheresis
- Promising treatment but several disadvantages:
  - ❖ Time and cost of travel for patients to have infusion
  - ❖ Won't work for every patient

LDL-C, Low-density lipoprotein cholesterol ; TE, technical engagement

Professional group perspectives

Link to main slides: summary

Submission from HEART UK – The Cholesterol Charity

Current treatment pathway:

- Unmet need for new treatments: current options don't reduce LDL-C to target levels:
  - ❖ Lomitapide: tolerability and liver function issues
  - ❖ Apheresis: challenges with venous access, geographical access (only 7 centres in UK), time burden (4-hour session every week), staff capacity at centres
- Aim: reduce onset & progression of CV disease, aortic root and cardiac valve disease
  - ❖ Positive outcome = ≥15% reduction in LDL-C (over biological variability)
  - ❖ Evidence that lowering LDL in HoFH improves outcomes, including mortality
- HoFH currently treated in selected 3° centres: evinacumab likely given in these settings with potential home administration if well tolerated

Benefits of evinacumab

- Of the 70-80 HoFH patients in UK, <50% likely need evinacumab (severe phenotype, intolerant to other therapies or can't access lipoprotein apheresis)
- Easier administration than other options (1hr infusion Q4W), effective & well tolerated in trials
  - ❖ Would use in high-risk patients, especially where apheresis +/- lomitapide not successful

CV, cardiovascular; LDL-C, Low-density lipoprotein cholesterol ; FH, familial hypercholesterolaemia; Q4W, every 4 weeks

Link to main slides: background

Decision problem

Lomitapide only comparator in adults; no comparator in 12 to17-year-olds

	Final scope	Company	EAG
Population	People with homozygous familial hypercholesterolaemia aged ≥12 years	Unchanged	Limited data for people aged 12-17
Intervention	Evinacumab as an adjunct to diet and other LDL-C lowering therapies	Unchanged	Consistent with MHRA
Comparator	**≥18-years:** Established clinical management without evinacumab (including but not limited to statins, diet and lifestyle changes, ezetimibe, lomitapide (>18 years only), evolocumab & LDL apheresis)	**≥18-years:** Lomitapide: evinacumab expected to replace in clinical practice. **12-17 years:** No comparator: limited comparative evidence (mostly single-armed data)	Company not considered treatment for people not on lomitapide (<18 years or due to toxicity)

MHRA, Medicines and Healthcare products Regulatory Agency; LDL-C, Low-density lipoprotein cholesterol

Key clinical trials (1)

Link to main slides: Clinical effectiveness

Company's pivotal trial: 24-week RCT vs. placebo & 24 week open-label extension period

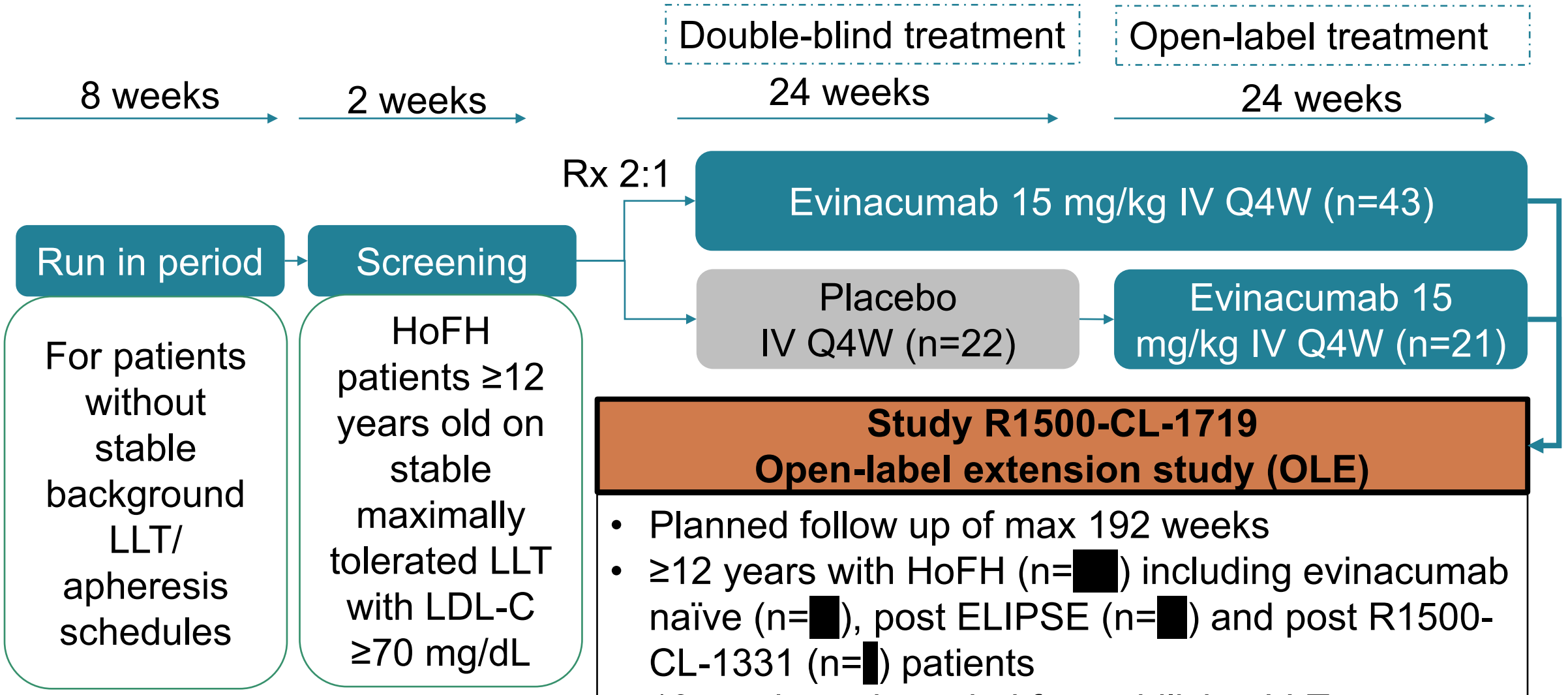
Clinical trial designs and outcomes

	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

ELIPSE study design

24-week double blind RCT period followed by 24 weeks open label evinacumab



Link to main slides: Clinical effectiveness

IV, intravenous; LDL-C, Low-density lipoprotein cholesterol; LLT, lipid lowering therapy; n, number; Q4W, every 4 weeks; RCT, randomised controlled trial

Key clinical trials (2)

Link to main slides: Clinical effectiveness

Supporting data for evinacumab from 2 single arm studies (proof of concept and OLE)

	R1500-CL-1331	R1500-CL-1719 (OLE)
Design	Open-label, single arm, proof of concept	Open-label, single arm
Population	≥18 years with HoFH	≥12 years old with HoFH on maximally tolerated LLTs (treatment naive or completed ELIPSE/R1500-CL-1331)
Technology	Starting: 250mg SC; Weeks 2-12: 15 mg/kg IV Q4W; weeks 12-15: 450 mg SC	15 mg/kg IV Q4W
Duration	15 weeks	192 weeks planned
1° outcome	% change in LDL-C to week 4	Safety
Key 2° outcomes	Absolute & % Δ in LDL-C, Apo B, non-HDL-C, TC, Lp(a); safety	Absolute & % Δ in LDL-C, Apo B, non-HDL-C, TC, TG; antibody status
Locations	Global (including Europe). No UK sites	
In model?	No – proof of concept: not discussed	No but useful for long-term effects

ApoB, Apolipoprotein B; HDL, high-density lipoprotein; IV, intravenous; LDL-C, Low-density lipoprotein cholesterol; Lp, lipoprotein; Q4W, every 4 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event; TC, total cholesterol; TG, triglycerides

Link to main slides : Clinical effectiveness

ELIPSE baseline characteristics

Few adolescents in trial; background therapies may not represent UK practice

	Evinacumab (n=43)	Placebo (n=22)
Age, years, mean (SD)	44 (17)	37 (12)
Aged ≥12 to <18	1 (2)	1 (5)
BMI, kg/m², mean (SD)	26 (6)	25 (6)
History of CHD, n (%)	38 (88)	21 (96)
Prior LLT, n (%)		
Statin	41 (95)	20 (91)
Ezetimibe	33 (77)	16 (73)
PCSK9 inhibitor	34 (79)	16 (73)
LDL apheresis	14 (33)	8 (36)
Lomitapide	11 (26)	3 (14)

EAG comments

- Only 2 adolescent patients: not reflective of company's positioning in pathway
- Statin, ezetimibe and LDL apheresis use may be higher in UK than in trial: representative of NHS population?
- 25% people on lomitapide as background therapy, including those having evinacumab: confounder?

Are these baseline characteristics generalisable to NHS clinical practice?

BMI, body mass index; CHD, coronary heart disease; LDL-C, Low-density lipoprotein-cholesterol ; PCSK, Proprotein convertase subtilisin/kexin; SD, standard deviation. Evinacumab and placebo given by IV Q4W

Clinical trial results: secondary endpoints

Improvements in key secondary outcomes with evinacumab vs. placebo

Δ in blood parameters from baseline	ELIPSE: week 24 LS mean difference vs. placebo (95% CI, p)	R1500-CL-1719 (OLE) Δ from baseline (Day 1 of OLE)	
		Week 24	Week 120
ApoB	-37% (-49 to -25); p<0.001	[redacted]	[redacted]
Non-HDL-C	-52% (-65 to -39); p<0.001	[redacted]	[redacted]
Total cholesterol	-48% (-59 to -38); p<0.001	[redacted]	[redacted]
Triglycerides	-50% (-66 to -35); p NR	[redacted]	[redacted]
Lp(a)	-2% (-16 to 12); p NR	NR	NR

Other key 2° outcomes	ELIPSE: week 24	
	Evinacumab	Placebo
% meeting US apheresis eligibility criteria at week 24*	7	23
	Difference: OR 0.1 (0 to 1); p0.09	
Mean Δ in utility to week 24 (SD)	-0.0189 (0.10926)	-0.0593 (0.16054)

ApoB, Apolipoprotein B; HDL-C, high-density lipoprotein-cholesterol; OR, odds ratio; SD, standard deviation. Odds ratio of <1 favours evinacumab.

Link to main slides: Clinical effectiveness

Adverse events

Link to main slides: Clinical effectiveness

TEAEs during the double bind treatment period of ELIPSE

Adverse event	Placebo (n=21)	Evinacumab (n=44)
% with any TEAE	17 (81%)	29 (66%)
% with ≥1 serious TEAE	0	2 (5%)
Treatment related AEs		
Site pruritus	0	2 (5%)
Nasopharyngitis	0	2 (5%)
Pyrexia	0	1 (2%)
Muscular weakness	0	1 (2%)
Epistaxis	0	1 (2%)
Gastroenteritis	0	1 (2%)
URTI	0	1 (2%)
Vascular pain	0	1 (2%)
Face oedema	1 (5%)	0
Hypoaesthesia	1 (5%)	0
Total	**1 (5%)**	**5 (11%)**

EAG comments

- No one had a TEAE that resulted in discontinuation or death
- No suspected major adverse cardiovascular events during the double-blind treatment period of ELIPSE.

AE, adverse event; TEAE, treatment-emergent adverse event.

Key issue: Reliability of the MAIC (3)

Differing efficacy of evinacumab dependant on analyses used

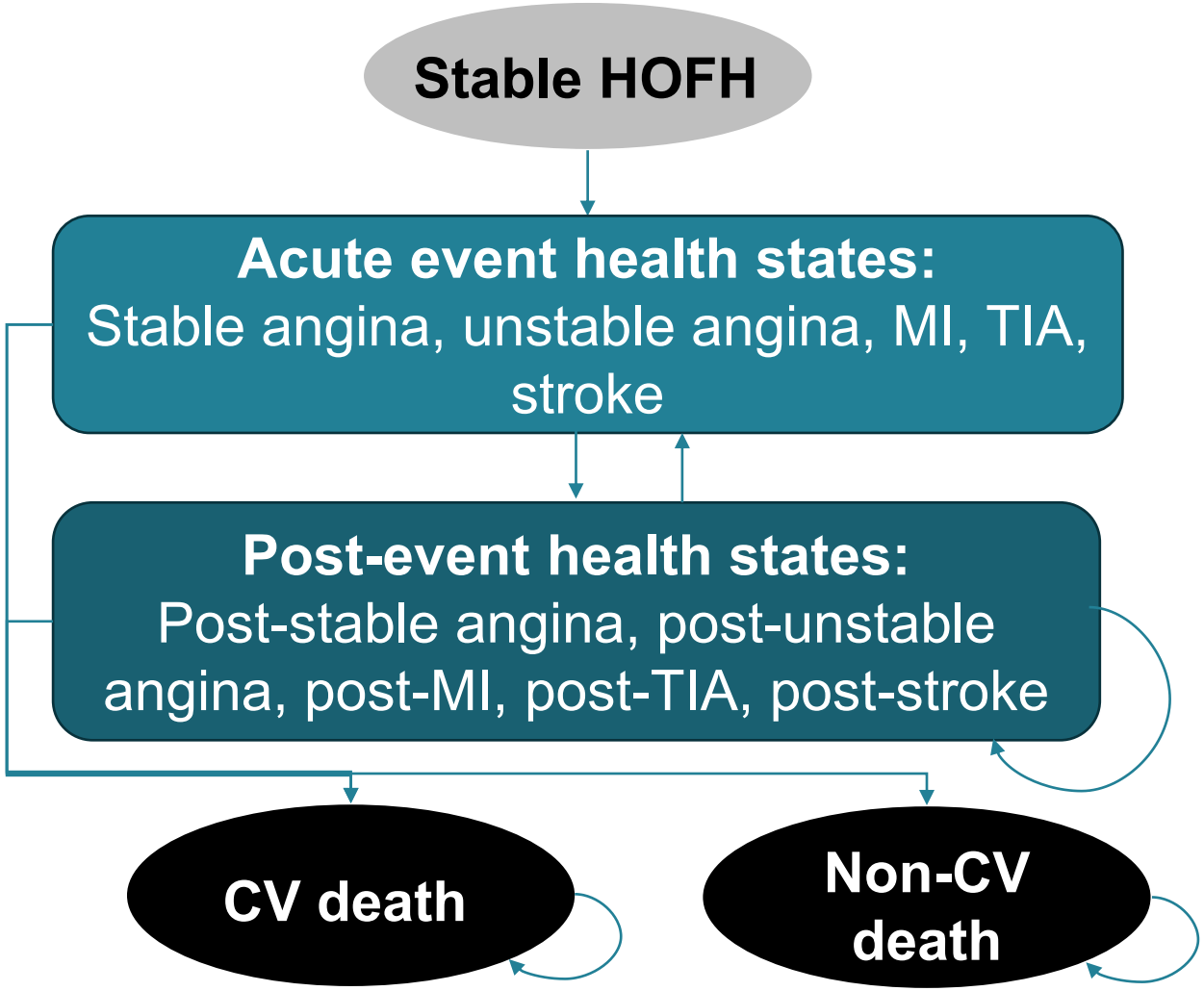
Analysis	N	Result
MAIC with lomitapide patients removed	ESS3.9	-33.83% (95% CI -29.2 to +96.8%)
Naïve data vs. placebo	65	-49.0% (95% CI -65.0 to -33.1%)
Naïve data vs. baseline, ELIPSE ***EAG base case***	43	-47.1% (95% CI -60.0 to -34.2%)
Cohort with lomitapide patients removed vs. placebo, ELIPSE	51	-50.9% (95% CI -58.8 to -42.0%)
Cohort with lomitapide patients removed vs. baseline	40	-46.4% (95% CI -56.4 to -36.4%)
Full MAIC as intended a priori ***Company base case***	ESS9.9	-55.1% (95% CI –71.90 to 38.27%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ESS, effective sample size; MAIC, matching adjusted indirect comparison; n, number; OLE, open label extension

Link to main slides: Clinical effectiveness

Company's model overview

De novo Markov model with acute and post event health states for 5 non-fatal CV events



- People enter model with no CV event history
- Transition to 1 of 5 non-fatal CV events
- Non-fatal events have acute- (1st year) and post- (year 2+) event health states: associated with different costs & benefits.
- After 1st acute event, transition to post-event state or experience another acute event (except stable angina and TIA)
- Transition to death from any health state

Affects costs & QALYs by: ↓ LDL-C which ↓ risk of fatal & non-fatal CV events:

- patients remain alive and in health states with ↑ HRQoL & ↓ costs.

Assumptions with the greatest ICER effect:

- source for treatment effect vs. lomitapide
- background LLT as a comparator
- treatment acquisition costs

CV, cardiovascular; ICER, incremental cost effectiveness ratio; HRQoL, health related quality of life; LDL-C, Low-density lipoprotein cholesterol; LLT, lipid lowering therapy MI, myocardial infarction; TIA, transient ischaemic attack.

Link to main slides: cost effectiveness

How company incorporated evidence into model

Main clinical inputs: ELIPSE, MAIC with lomitapide and a paper by Thompson et al.

Parameter	Description
Structure	Markov model with acute & post event health states for 5 non-fatal CV events
Intervention	Evinacumab 15mg/kg IV Q4W
Comparator	Lomitapide 10-60mg OD. Dose depends on time on treatment & AEs
Baseline characteristics	• Age, BMI, weight, sex, mutation status: ELIPSE • No prior CV events assumed (1° prevention patients only) • LDL-C: Thompson et al. adjusted to background treatment mix in ELIPSE
CV progression	• Time to CV death: Thompson *et al*. extrapolated using Gompertz curve • Distribution of CV events: Thompson *et al*. and Ward et al.
Treatment efficacy	Reduction in LDL-C: MAIC Relationship between LDL-C and CV risk: CTTC meta-analysis
Recurrent CV events	Ward et al.
Health state utility values	• Stable HoFH: Ara & Brazier. 2010 age- and sex-adjusted based on ELIPSE baseline characteristics • Acute- and post-event health states: TA694 • Apheresis: disutility for haemodialysis from Beaudet *et al*. 2014

CV, cardiovascular; LDL-C, Low-density lipoprotein-cholesterol

Link to main slides: cost effectiveness

Key issue #4: Primary vs. secondary prevention patients

Company: prior CV events not included as lack of clinical data and complex to model

Background: Company's model assumes no prior CV events (1° prevention patients only)

- People can only experience or have health-consequences from one CV event per year

Company:

- Model structure aligned with concepts from other TAs in CV conditions
- Not possible to model prior CV events without increasing model complexity
- HoFH ultra-rare: limited data to inform modelling. Model simple to avoid inappropriate extrapolation
- Amending number of 2° prevention patients affects both model arms -> limited effect on ICER

***Scenario*:** 50% enter model with stable HoFH (1° prevention patients), 50% distributed to post-event health states (2° prevention patients)

Clinical expert: not correct to consider 1° and 2° prevention patients as binary outcomes

- Even if patient not had MI, will undoubtably have atherosclerotic disease and should be treated aggressively.

CV, cardiovascular; ICER, incremental cost effectiveness ratio; MI, myocardial infarction; TA, technology appraisal

Link to main slides: other key issues

Key issue #4: Primary vs. secondary prevention patients

EAG: critical oversight not to capture difference between 1° & 2° prevention patients

EAG:

- Robust data shows different outcomes for 1st and subsequent CV events
- Many HoFH patients likely have CV events before 42 years (model starting age):
  - ELIPSE patients at baseline (average age in evinacumab arm = 44):
    - N=34 (52%) had prior history of CHD, N=59 (91%) had any CV history/risk factors
  - Company should use % 1° & 2° prevention patients from ELIPSE for model baseline
- Clinical experts: ~70% 2° prevention patients in NHS practice (***EAG base case***)
- Company's scenario simplistic: same utility and cost for 1st & subsequent CV events
  - ***EAG scenario:*** adjusted stable HoFH utility for 2° prevention patients, using weighted average of post-event health states in base case
- Other TAs modelled subsequent CV events (e.g. TA694: separate states for 1°, 2° & 3° CV events)

EAG and company scenarios

	% 2° prevention*
Company base case	**0%**
Company scenario	50%
EAG base case	70%
EAG scenario	100% + adjusted utilities

*2° prevention patients distributed across post-event health states unless specified

What is the committee's preference for modelling cardiovascular events?

CHD, Coronary heart disease; CV, cardiovascular; N, number; TA, technology appraisal

Link to main slides: other key issues

Key issue #4: Primary vs. secondary prevention patients

EAG scenario adjusts stable HoFH utility value to account for impact of prior CV events

Health state utility values for company & EAG base cases and EAG adjusted utility values for 2° prevention patients

Health state	Base case utilities: 1° prevention (no prior CV history) at baseline			2° prevention and successive event utilities scenario*		
	Baseline	Acute event	Post event	Baseline (scenario)	Acute event + prior CV condition	Post event + prior 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

*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. Acute event: event <12 months. Post event: no event <12 months

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

Link to main slides: other key issues

Key issue #5: Cardiovascular mortality (CVM)

Link to main slides: other key issues

EAG: Thompson et al. may overestimate CVM; presented scenarios with lower CVM risk

Background: mortality not captured in ELIPSE: CVM in company model from Thompson *et al.* (2018): retrospective study between 1964 and 2014 including 44 UK HoFH patients.

- Time to CVM estimated using parametric models -> Gompertz chosen for best fit

EAG: *Thompson et al. overestimates CVM:*
Differences between those alive and dead at end of study. People alive had:

- access to statins earlier and for longer
- more frequent & effective LDL apheresis (improved techniques)
- ↓ mean on-treatment TC (8.1 vs 14.5 mmol/L)

Prefer CVM estimates from HoFH patients than general public but can't calculate using only alive patients at end of study in Thompson et al.

- ***Base case:*** CVM risks using Gompertz
- ***Scenario:*** CVM using Weibull (2nd best fit, ↓ CVM risk)

Company: limited HoFH natural history data

- ELIPSE represents current pathway but can't use to estimate CVM risk
- Thompson et al: UK & HoFH specific and reported IPD
- Other sources of CVM not generalisable

Mitigate uncertainty from pre-statin patients by applying separate background LLT effects (key issue #6)

Clinical experts: Thompson et al mostly UK patients: generalisable to NHS

CVM, cardiovascular mortality; IPD, individual patient data; LDL-C, Low-density lipoprotein-cholesterol; LLT, lipid lowering therapy; MA, marketing authorisation

Key issue #6: Baseline LDL-C for background LLT

Company's baseline LDL-C based on Thompson et al. adjusted for ELIPSE population

Background:

Figure and table: company's approach to calculating baseline LDL-C

Thompson et al. baseline LDL-C = 8.71 mmol/L → Calculated difference in baseline LLT use between studies → Treatment effects applied as weighted average of difference in LLT use between studies → Modelled baseline LDL-C = **7.93 mmol/L**

Treatment	% in ELIPSE*	Difference vs. Thompson et al	Efficacy	Source
Atorvastatin†	93.8%	+5.2%	-20.0%	SPC, clinical trial
Ezetimibe†	75.4%	+4.9%	-20.7%	Company MAIC (Gagne et al. 2002)
Evolocumab†	76.9%	+76.9%	-30.8%	Bucher's ITC (TESLA B study)
LDL- apheresis	33.8%	-25.2%	-30.7%	Retrospective cohort study

*Reflects % having these background treatments in model. † Not applied to people with null/null mutations (32.3%)

Company: Thompson et al. chosen to align with baseline CVM source (see key issue #5) but adjusted for ELIPSE background LLTs to reflect current practice

CVM, cardiovascular mortality; ITC, indirect treatment comparison; LDL-C, Low-density lipoprotein cholesterol ; LLT, lipid lowering therapy; MAIC, matching adjusted indirect comparison; SPC, summary of product characteristics

Link to main slides: other key issues

Key issue #6: Baseline LDL-C for background LLT

EAG: company's baseline LDL-C may be overestimated

EAG comments: company's approach introduces uncertainty and lacks robustness:

- Model overestimates LDL-C for the following parameters:

Parameter	Company's model	ELIPSE	Difference
Baseline LDL-C	7.9 mmol/L	6.6 mmol/L	18%
Reduction in LDL-C with evinacumab	4.4 mmol/L	3.5 mmol/L	25%

- Efficacies for LLTs highly uncertain: adding each individually adds to uncertainty inherent in calculated treatment effect
- Uncertainty in MAIC (key issue #2): inappropriate to use results for LLT treatment effects
- Agree ELIPSE best source of background LLT data but:
  - ❖ Can't directly apply treatment effect on LDL-C from MAIC with lomitapide as doesn't capture correlation between LDL-C and CVM
  - ❖ **Base case (post TE):** baseline LDL-C 6.6 (difference in LDL-C between ELIPSE and Thompson et al. applied to treatment effects)

What is the committee's preferred approach to modelling baseline LDL-C?

CVM, cardiovascular mortality; LDL-C, Low-density lipoprotein cholesterol; MAIC, matching adjusted indirect comparison

Link to main slides: other key issues

Other differing assumptions in company & EAG base cases

Assumption	Company base case	EAG base case	Impact
Utility multipliers for MI & post TIA	Company's original utility values in TA694, age- and sex-adjusted for ELIPSE patients (MI = 0.783, post TIA = 0.994)	TA694 committee preferred utility values, age-and sex-adjusted for ELIPSE patients (MI =0.721, post-TIA =0.78)	
Evinacumab costs	£552 for all years	Longer nurse time needed for first IV infusion: £621 1st year, £552 years 2+	
LDL-apheresis stopping rate	10.34% (% stopping in Cuchel et al. 2013 in the full ITT population)	16.67% (% stopping in Cuchel et al. 2013 who had LDL-apheresis)	
Monitoring costs	• GP visit and blood test costs: CG181 • Lomitapide: 3 liver monitoring tests and a Fibroscan® test annually	• GP visit and blood test costs: PSSRU 2022 • Lomitapide: SmPC monitoring recommendations (including monthly liver monitoring tests in the first year)	
Health state costs	• 2018 inflated costs from TA694 inflated again to 2022 using ONS CPI inflation indices • Death: company submission in TA694	• Primary source costs in TA694 inflated to 2022 using ONS CPI inflation indices • Death: EAG preferred cost in TA694 (from CG181)	

 Large change: >£10,000 per QALY gained

 Minimal change: <£5,000 per QALY gained

CG, clinical guideline; ITT, intention to treat; LDL-C, Low-density lipoprotein cholesterol; MI, myocardial infarction; ONS CPI, Office for National Statistics Consumer Prices Index; PSSRU, Personal Social Services Research Unit; SmPC, Summary of product characteristics; TA, technology appraisal; TIA, transient ischaemic attack

Key EAG scenarios

Interventions	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Evinacumab vs lomitapide			
EAG base case (MAIC excluding lomitapide treated evinacumab patients)	SW quadrant: see Part 2 slides		
MAIC including lomitapide treated evinacumab patients	↑ Increases	↑ Increases	Cost effective
Adolescent population: LLTs from 12 to 18 years old, then lomitapide	↑ Increases	↑ Increases	NW quadrant (dominated)
All patients are secondary prevention	↓ Decreases	↑ Increases	SW quadrant
CV mortality using the Weibull distribution	↑ Increases	↓ Decreases	SW quadrant
Company's approach to baseline LDL-C	↓ Decreases	↓ Decreases	SW quadrant
Evinacumab vs LLT			
ELIPSE treatment effects	↑ Increases	↑ Increases	Over 30,000

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.

Link to main slides: key cost effectiveness scenarios