

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia [ID1647]

**Part 1
slides**

Lead team presentation

1st appraisal meeting - Committee C

Chair: Stephen O'Brien

Lead team: Kiran Moyo, Andrea Manca, Stella O'Brien

Technical team: Alan Moore, Nicola Hay, Linda Landells

Company: Novartis

ERG: Warwick Evidence

11th May 2021

Abbreviations

Abbreviation	
ALI	Alirocumab
ASCVD	Atherosclerotic cardiovascular disease
ASCVD-RE	Atherosclerotic cardiovascular disease – risk equivalents
CV	Cardiovascular
CVD	Cardiovascular disease
CPRD	Clinical Practice Research Datalink
CTT	Cholesterol Treatment Trialists (dataset)
EVO	Evolocumab
EZE	Ezetimibe
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
IS	Ischemic stroke

Abbreviation	
LDL-C	Low-density lipoprotein cholesterol
LLTs	Lipid lowering therapies
LS	Least squares
MI	Myocardial infarction
mmol/L	millimoles per litre
NA	Not applicable
NF	Non-fatal
NR	Not reported
NMA	Network meta-analysis
MTS/MTD	Maximum tolerated statins/ Maximum tolerated dose
PAD	Peripheral arterial disease
PCSK9i	Proprotein convertase subtilisin/kexin type 9 inhibitor
PPER	Primary prevention elevated risk
Revas	Revascularisation
RR	Rate ratio
SA	Stable angina
THIN	The Health Improvement Network
TIA	Transient ischemic attack
UA	Unstable angina

NICE

Commonly used abbreviations in bold

Primary hypercholesterolaemia and mixed dyslipidaemia

Overview of the condition

- Hypercholesterolaemia is the presence of increased levels of cholesterol (primarily low-density lipoprotein; LDL-C) in the blood
 - Familial hypercholesterolaemia (FH) is inherited with most people manifesting the heterozygous form (HeFH)
 - Non-familial hypercholesterolaemia (non-FH) has no specific genetic cause
- Mixed dyslipidaemia is defined as a combination of increased levels of LDL-C and triglyceride levels, and may include decreased levels of high-density lipoprotein (HDL-C)
- LDL-C is known to be a major causal risk factor for Atherosclerotic Cardiovascular Disease (ASCVD)
- Primary prevention population refers to people who have not experienced a CVD event. Secondary prevention population refers to people who have experienced a CVD event

Inclisiran (Leqvio, Novartis)

Description of technology	<p>Double-stranded small interfering RNA, conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. Leads to a reduction of intrahepatic PCSK9 levels, thereby increasing LDL-C uptake and lowering LDL-C levels</p>
Marketing authorisation (received December 2020)	<p>Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:</p> <ul style="list-style-type: none"> • in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or • alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
Dosage and administration	<p>284 mg administered as a single subcutaneous injection: initially, again at 3 months and then every 6 months.</p>
Price	<p>***** per 284 mg dose pack. 1st year costs: *****, subsequent year costs: ***** ***** (commercial access agreement agreed in principle)</p>

Recent NICE appraisals in primary hypercholesterolaemia and mixed dyslipidaemia

TA	Recommendation
385 – Ezetimibe (EZE) ^{a,*} [2016]	<ul style="list-style-type: none"> ➤ Recommended as monotherapy in those for whom statin therapy is contraindicated. ➤ Recommended as monotherapy in those who are statin intolerant. ➤ Recommended with initial statin therapy if insufficient response to statin.
393 – Alirocumab (ALI)** [2016]	<ul style="list-style-type: none"> ➤ Recommended for those who are statin intolerant, with or without previous EZE. ➤ Recommended for those who have had insufficient response to statin, with or without previous EZE + statin.
394 – Evolocumab (EVO)** [2016]	<ul style="list-style-type: none"> ➤ Recommended for those who are statin intolerant, with or without previous EZE. ➤ Recommended for those who have had insufficient response to statin, with or without previous EZE + statin.
694 - Bempedoic acid with ezetimibe [2021]	<ul style="list-style-type: none"> ➤ Recommended when statins are contraindicated or not tolerated, and EZE alone does not control low-density lipoprotein cholesterol well enough.

Recommendation of PCSK9i: Alirocumab (TA393) and evolocumab (TA394)

LDL-C concentrations above which ALI and EVO are recommended	Without CVD	With CVD	
		High risk of CVD ¹	Very high risk of CVD ²
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/L	Recommended only if LDL-C concentration is persistently above 3.5 mmol/L
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/L	Recommended only if LDL-C concentration is persistently above 3.5 mmol/L	

¹High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, peripheral arterial disease.

²Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Patient and carer perspectives

Thank you to HEART UK, for their submission

Living with the condition + current care

- Most people have no symptoms. NHS Health Checks are offered to prevent future CVD events
- Care is delivered inconsistently across NHS
- Adults may be reluctant to express treatment doubts and stop engaging
 - statin intolerance a concern
 - many do not progress through the treatment pathway

Unmet need

- CVD underlying cause of 26% of all deaths in UK. 160,000 deaths yearly
 - 42,000 deaths occur prematurely and may be preventable in many cases
- >50% of adults need to manage cholesterol
- Current therapies are effective but access and adherence are poor
 - PCSK9i treatments (underused and subject to strict criteria)

Inclisiran

- Twice-yearly treatment in primary care is more accessible than specialist settings
 - genetic testing not available in primary care
 - adherence would improve
- Longer term benefits much greater than current treatments

Equalities considerations

- People in most deprived areas almost 4 times as likely to die prematurely from CVD
 - overweight/obesity, more prevalent in deprived areas
- People with severe mental illness and learning disabilities at increased CVD risk
- Minority groups

Professional perspectives

Thank you to clinical experts, Primary Care Cardiovascular Society, and British Cardiovascular Society for their submissions

Treatment aim

- To lower LDL-C (in people with ASCVD or at risk of ASCVD)
- Aim is not to overtreat low-risk or undertreat high-risk populations
- Reduce CV mortality and morbidity
- Reducing LDL-C shown to reduce risks of CVD events (1 mmol/L reduction = 21% reduction in risk)

Treatment pathway

- Secondary prevention pathway well defined: high intensity statin, possibly also ezetimibe, not commonly started on PCSK9is
- In secondary care most specialists would add ezetimibe as standard of care (usually added in primary care for statin intolerance)
- Referral from primary care usually only if statin intolerant (less commonly when LDL-C deemed too high, 2.6 mmol/L might not be seen as high enough in primary care).

Unmet need

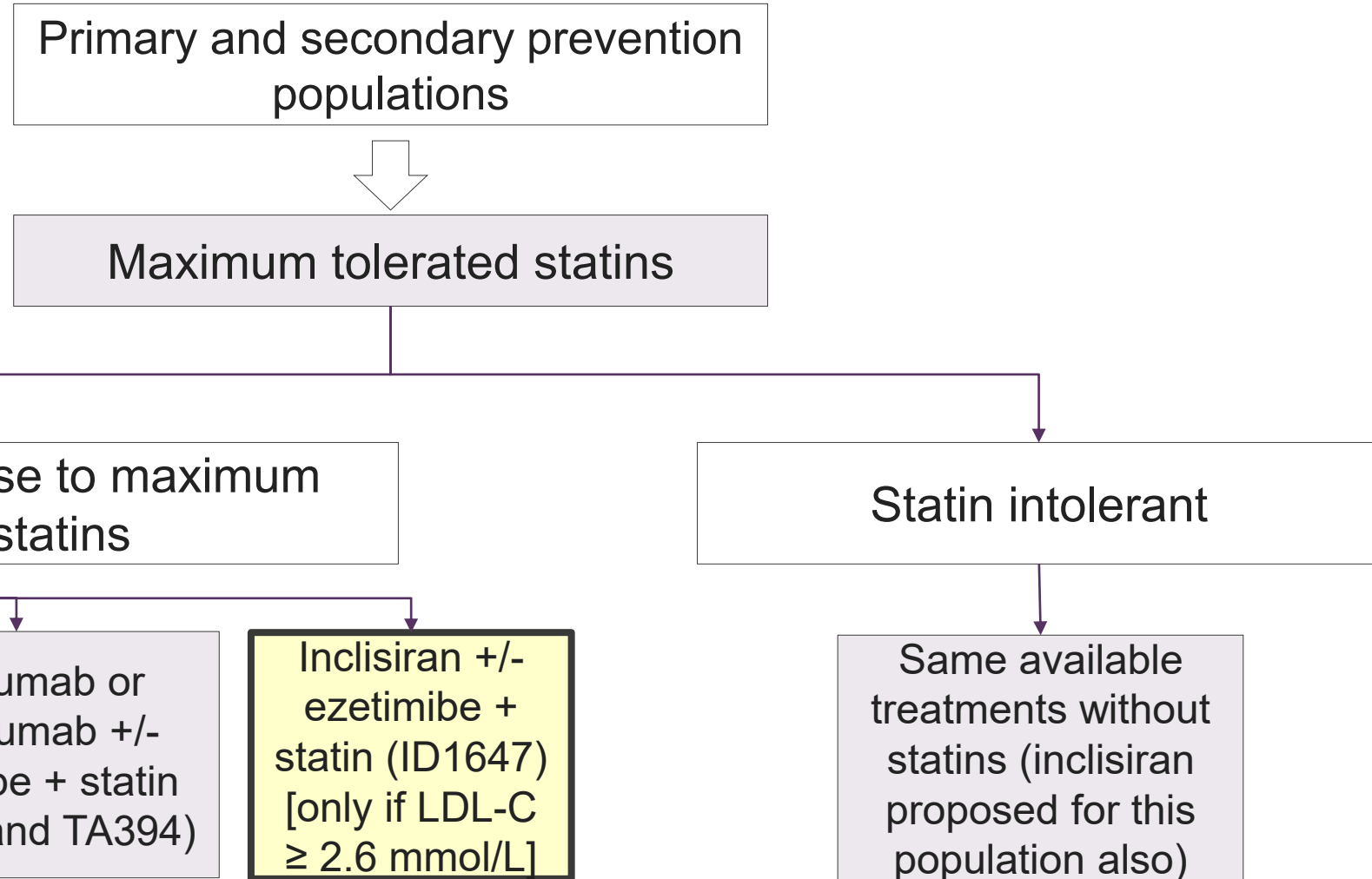
- Lowering LDL-C to <2.6 mmol/L a suitable target, difficult to achieve with current oral treatments (statins and ezetimibe)
- PCSK9i eligibility criteria means many do not reach LDL-C goals
- Considerable number of people eligible for PCSK9i in primary care not being referred
- Condition is poorly treated

Inclisiran

- Would help a greater % reach lipid targets. Fewer prescriptions/dispensing encounters
- No specific significant extra monitoring
- Lower eligibility threshold and primary care setting = more treatment access
- Primary care ideally placed to find, assess and manage eligible population
- Twice yearly administration by healthcare professional means increased compliance

Treatment pathway – hypercholesterolaemia

Overview of the treatment pathway based on previous NICE TAs and proposed positioning of inclisiran



NICE

Alirocumab and evolocumab (TA393/TA394) recommendations:

- Secondary prevention (high-risk) only if LDL-C levels > 4 mmol/L
- Secondary prevention (very high-risk) only if LDL-C levels > 3.5 mmol/L
- Primary prevention HeFH only if LDL-C levels >5 mmol/L

Populations included in company submission

NICE Scope included the following pathway positions: vs MTS, after MTS and after MTS + EZE

Company base case: 3 populations - all have **LDL-C ≥ 2.6 mmol/L** and separated by secondary prevention (after ASCVD event) and primary prevention (before ASCVD event)

2.6 mmol/l threshold rationale: Greater risk reduction with LDL-C ≥ 2.6 mmol/L in ODYSSEY outcomes trial (alirocumab), similar to mean baseline levels in ORION-10/11 and supported by clinical experts

Secondary Prevention

Population 1: Secondary prevention population; ASCVD (including HeFH) with LDL-C ≥ 2.6 mmol/L despite MTS

Primary Prevention

Population 2: Primary prevention population*; Elevated risk (PPER*) with LDL-C ≥ 2.6 mmol/L despite MTS

Population 3: Primary prevention population; HeFH with LDL-C ≥ 2.6 mmol/L despite MTS

Available treatments and eligibility criteria by each population

Ezetimibe:
all LDL-C levels

(company do not consider EZE to be a comparator)

Alirocumab or Evolocumab:
High Risk of CVD: **LDL-C > 4 mmol/L**
Very High Risk of CVD: **LDL-C > 3.5 mmol/L**
ASCVD with HeFH: **LDL-C > 3.5 mmol/L**

Alirocumab or Evolocumab:
Not recommended at any LDL-C level

Alirocumab or Evolocumab:
LDL-C > 5.0 mmol/L

EZE: ezetimibe, MTS: maximum tolerated statins

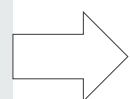
* individuals categorised as PPER (primary prevention elevated risk) if LDL-C levels ≥ 2.6 mmol/L, plus any of the following: type 2 diabetes (65.0% in ORION-11) or HeFH (14.8%) or 10-year ASCVD risk of $\geq 20\%$: Framingham risk score or equivalent (20.2%).

Population: Subgroups

Company also provide subgroup analyses for each of its 3 base case populations based on LDL-C level, statin intolerance and HeFH

Subgroups presented and ALI/EVO eligibility criteria (EZE recommended in all subgroup populations)

Population 1: Secondary prevention population; ASCVD (including HeFH) with LDL-C ≥ 2.6 mmol/L despite MTS

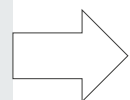


HeFH
(ALI/EVO:
LDL-C > 3.5
mmol/L)

LDL-C level:
 ≥ 4.0 and ≥ 3.5 mmol/L
(very high risk)
ALI/EVO: matches
subgroup LDL-C

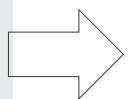
Statin intolerant
ALI/EVO:
recommendations
do not differ by
this subgroup

Population 2: Primary prevention population; elevated risk (PPER) with LDL-C ≥ 2.6 mmol/L despite MTS



Statin intolerant
ALI/EVO: not
recommended at
any LDL-C level

Population 3: Primary prevention population; HeFH with LDL-C ≥ 2.6 mmol/L despite MTS



LDL-C level:
 ≥ 3.0 , ≥ 4.0 and ≥ 5.0 mmol/L
ALI/EVO: only
recommended at LDL-C
 ≥ 5.0 mmol/L

Statin intolerant
ALI/EVO:
recommendations
do not differ by
this subgroup

Company also provide cost-effectiveness results for people by PCSK9i eligible/ineligible populations

NICE *all subgroups include people with LDL-C ≥ 2.6 mmol/l unless stated*

Evidence from ORION 9, ORION 10 and ORION 11

Main evidence for inclisiran comes from 3 clinical trials, summarised below:

	ORION-9 (n=482)	ORION-10 (n=1561)	ORION-11 (n=1617)
Description	Randomised, double blind, placebo-controlled, Phase III trial		
Duration	18 months (540 days)		
Intervention and comparator	Inclisiran 284 mg (single subcutaneous injection every 6 months after an initial dose (day 1) and another dose after 3 months). Placebo comparator		
Population (Adults)	HeFH and elevated LDL-C (≥ 2.6 mmol/L)	ASCVD and elevated LDL-C (≥ 1.8 mmol/L)	ASCVD or ASCVD-RE (PPER) and elevated LDL-C (≥ 1.8 mmol/L for ASCVD, ≥ 2.6 mmol/L for ASCVD-RE)
Background therapy*	Maximum tolerated statins or statin intolerant	Maximum tolerated statins or statin intolerant	Maximum tolerated statins or statin intolerant
Key results: mean % LDL-C change (95% CI) Baseline to 510 days (co-primary endpoint**)	-47.9 (-53.5, -42.3) p=<0.001	-52.3 (-55.7, -48.8) p=<0.001	-49.9 (-53.1, -46.6) p=<0.001

NICE *background ezetimibe use was also permitted

** other co-primary trial endpoint was time-adjusted LDL-C % change day 90 and up to day 540

Ongoing inclisiran clinical trials

Summary of current ongoing inclisiran trials

	ORION-4 (est: n=15,000)	ORION-8 (n= 2,991)
Description	Phase III RCT	Open-label extension of ORION-9/ ORION-10/ ORION-11
Intervention and comparator	Inclisiran v placebo	Inclisiran (single group)
Population (Adults)	ASCVD	ASCVD, ASCVD-RE, HeFH
Primary outcomes	Major CV events, CV deaths	LDL-C targets, LDL-C levels
Follow-up	Median of 5 years	Up to 3 years
Results expected	2026	2023

HeFH: Heterozygous familial hypercholesterolaemia

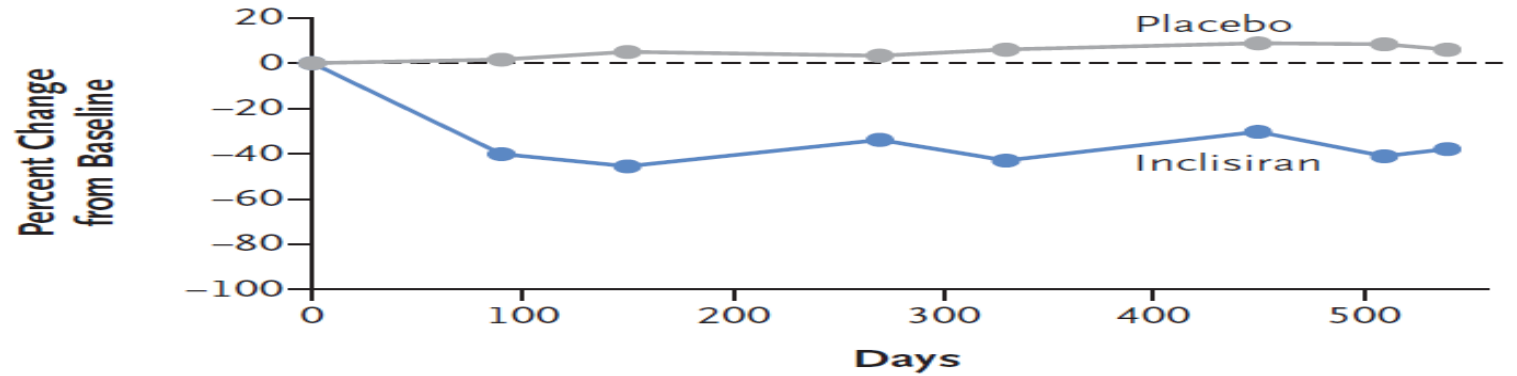
ASCVD: Atherosclerotic cardiovascular disease

ASCVD-RE: Atherosclerotic cardiovascular disease – risk equivalents

NICE The SPIRIT trial is also ongoing (est n=900) evaluating use of inclisiran in a primary care setting (NHS) with a 9 month follow-up (ASCVD and ASCVD-Risk Equivalent)

Clinical effectiveness results: ORION-9/ORION-10/ORION-11

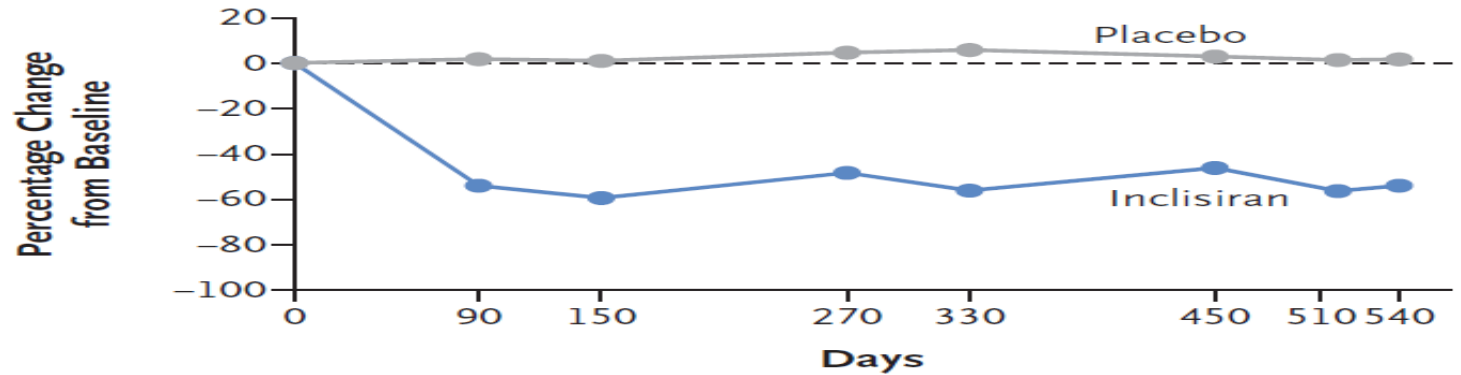
**ORION-9 mean %
LDL-C change
HeFH**



No. of Patients

Placebo	240	237	238	235	233	233	229	232
Inclisiran	242	240	239	240	237	237	231	232

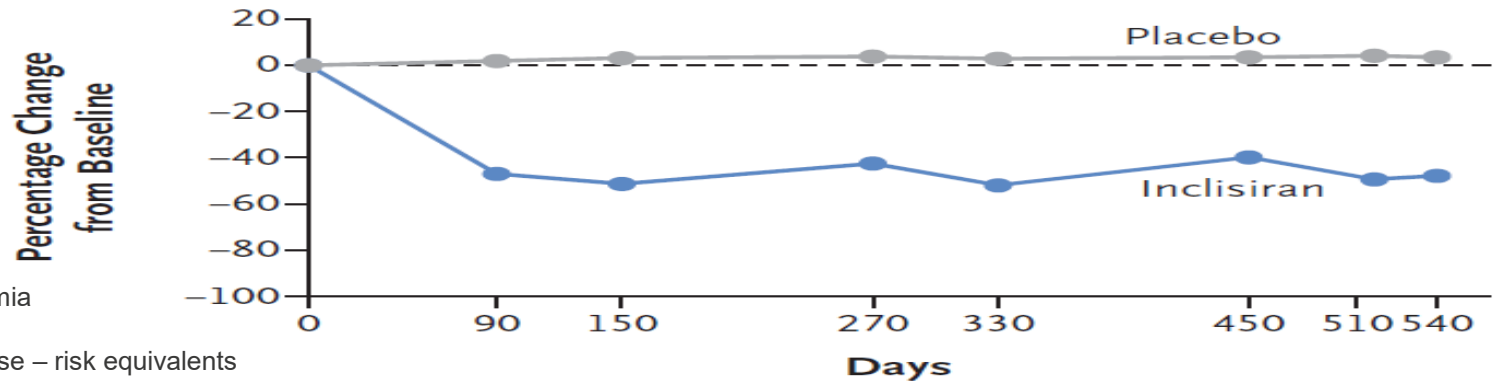
**ORION-10 mean %
LDL-C change
ASCVD**



No. of Patients

Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

**ORION-11 mean %
LDL-C change
ASCVD and
ASCVD-RE**



HeFH: Heterozygous familial hypercholesterolaemia
ASCVD: Atherosclerotic cardiovascular disease
ASCVD-RE: Atherosclerotic cardiovascular disease – risk equivalents

NICE

No. of Patients

Placebo	807	797	785	774	773	764	739	749
Inclisiran	810	790	796	778	773	768	724	742

Network Meta-Analysis (NMA)

There are no head-to-head trials. The company undertook NMAs to compare inclisiran with alirocumab, evolocumab, ezetimibe through a common placebo comparator. ERG agreed methods were appropriate.

3 NMAs conducted (ASCVD/PPER MTD, ASCVD/PPER statin intolerant and HeFH MTD).

NMA results

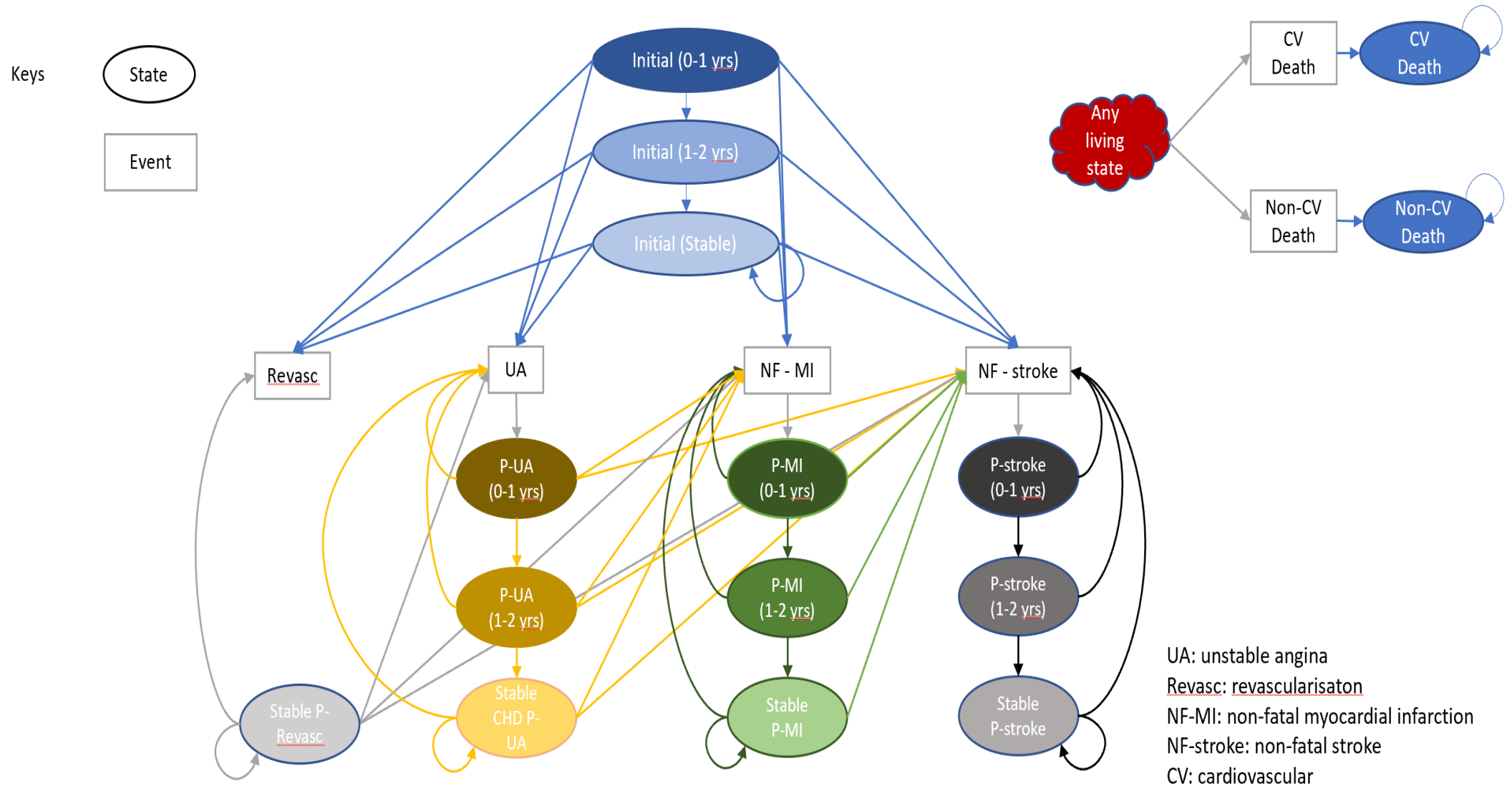
Inclisiran vs	ASCVD/PPER MTD		ASCVD/PPER statin intolerant		HeFH MTD	
	Mean difference (95% CrI)	Probability (inclisiran better than comparator)	Mean difference (95% CrI)	Probability (inclisiran better than comparator)	Mean difference (95% CrI)	Probability (inclisiran better than comparator)
Percentage change in LDL-C v comparator at						
PBO	*****	*****	*****	*****	*****	*****
ALI	*****	*****	*****	*****	*****	*****
EVO	*****	*****	*****	*****	*****	*****
EZE	*****	*****	*****	*****	*****	*****

NICE

*no ezetimibe trial data found for HeFH MTD NMA

HeFH: Heterozygous familial hypercholesterolaemia
 ASCVD: Atherosclerotic cardiovascular disease
 ASCVD-RE: Atherosclerotic cardiovascular disease – risk equivalents
 MTD: maximum tolerated dose

Summary of economic model (1)



- Markov cohort model based on TA393 (key difference: partitioning of acute coronary syndrome (ACS) health state into MI (myocardial infarction) and UA (unstable angina) states: more accurate measures of benefits/costs. 1 year cycle length and lifetime time horizon used. 3.5% discount rate.
- 15 health states: Initial (0-1; 1-2; 2+ years), post-event states for revascularisation, unstable angina (UA) (0-1; 1-2; 2+ years), non-fatal myocardial infarction (NI-MI) (0-1; 1-2; 2+ years), non-fatal stroke, cardiovascular death and non-cardiovascular death.

Summary of economic model (2)

Parameter	Source	ERG comment
Baseline characteristics (age, % male, % diabetes)	ORION clinical trials	Methods appropriate. ERG provide scenario analysis to determine impact of subpopulation weighting in ASCVD population (Using THIN database: TA393)
Baseline LDL-C	ORION clinical trials	Source is appropriate
Baseline CV risk	CPRD database (with Mohrschladt 2004 and Beliard 2018 used for ASCVD HeFH population)	Sources are appropriate – scenario analysis for ASCVD HeFH population using Beliard 2018 is appropriate
Rate ratios for CV events per mmol/L reduction in LDL-C	CTT meta-analysis	Updated CTT analysis used in previous NICE appraisals and appropriate
Treatment efficacy (LDL-C reduction)	Company NMAs	Appropriate, alternative scenarios provided using ORION trial outcome for inclisiran
Health utility	TA393 utility values used for CVD events	Appropriate
Costs of CV events	NICE CG181, NHS reference costs and TA393	Appropriate and scenario analysis provided using TA393 costs (little impact on ICER)
Adverse events	Not considered in model	Addition of disutility/cost would not have a major impact on the ICER

Key issues



Unknown impact



Small impact








Model driver










For discussion



Resolved

Issue	Company base case	ERG comments	Impact
Main Issue: Ezetimibe as part of standard of care or a relevant comparator	Do not consider ezetimibe to be a relevant comparator	Ezetimibe is a relevant comparator and disagree with company	
Additional issue 1: Generalisability of results from ORION-9 and ORION-10	Company use data from ORION-9, ORION-10 and ORION-11	Overall, trials appear generalisable, however they excluded people with ASCVD event in last 3 months	
Additional issue 2: lack of genetic testing = some familial HeFH cases missed	Company acknowledge lack of genetic testing.	Unknown impact: ERG has no issues with company approach regarding issue	
Additional issue 3: lack of scenario analysis using event rates from Beliard 2018 (ASCVD HeFH population)	Company provide scenario analysis using Beliard 2018 for ASCVD with HeFH population	Beliard scenario is more appropriate for ASCVD HeFH. Small impact on cost-effectiveness results	
Additional issue 4: Impact of differences in CV risk and severity of patients within each population on relative effects observed (LDL-C, HDL-C, discontinuations)	Meta-analyses by common trial criteria/baseline CV risk not feasible. Provide analysis exploring impact of baseline LDL-C on ASCVD/RE NMA.	Do not agree with company assumption that differences in severity/CV risk would not impact on efficacy. Lack of evidence to inform this issue.	

Issues raised by stakeholders during technical engagement

Issue	Description	ERG comments	Impact
<p>Populations and baseline LDL-C</p>	<p>Company base case population includes people eligible or ineligible for ALI/EVO. Company provide analysis by ALI/EVO eligibility</p>	<p>Base case population for ASCVD based on a mean LDL-C of 3.47 mmol/L – which is close to the thresholds for ALI/EVO</p>	 
<p>Treatment pathway/ primary care setting</p>	<p>Company propose inclisiran would be used in a primary care setting</p>	<p>No comments. In general, submissions and technical engagement responses support primary care use, but some concerns raised</p>	
<p>NMA (time point used and robustness)</p>	<p>Choice of timepoint used in the company’s NMA may impact inclisiran efficacy estimates. *****</p>	<p>Scenario analyses use alternative NMA timepoints. ***** selected due to most reported timepoint in NMA trials</p>	 
<p>Lack of longer term data and assumptions used</p>	<p>Lack of longer term outcome data for inclisiran (>18 months). Immediate benefit and no waning of efficacy assumed in model</p>	<p>Company could have provided a waning scenario (due to lack of longer term evidence). Note TA393/TA394 assumed no waning of treatment effect</p>	 

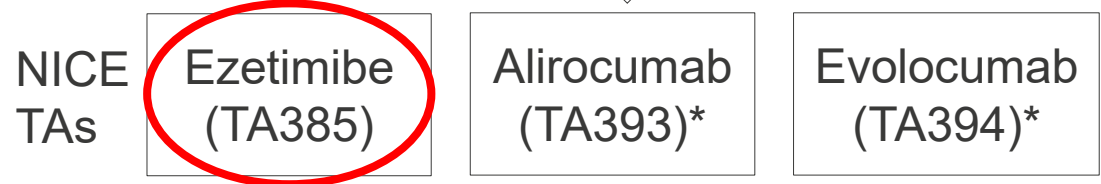
Key Issue: Ezetimibe

Part of standard care or a comparator?

Background

Company: EZE not a comparator to inclisiran. Company consider standard of care (SoC) to be "a population-specific mix of maximally tolerated statins (including no statins in patients who are contraindicated/intolerant) and other lipid-lowering therapy, including EZE": removing EZE as a comparator.

Maximum tolerated statins (or SoC) fail to control LDL-C and LDL-C ≥2.6 mmol/L



*Only recommended at certain LDL-C thresholds: see previous slides

Company

EZE not a relevant comparator because:

- Low use in NHS practice (4.1% ASCVD, 1.5% PPER, 5.4% HeFH; CPRD database)
- Clinical expert feedback: EZE use counter-productive: LDL-C reduction prevents access to advanced therapies (PCSK9i).

ERG

EZE is a relevant comparator because:

- CPRD database shows [REDACTED]
- ERG clinical experts: if LDL-C too high after MTS, decision to either switch to rosuvastatin (not yet generic) or add EZE; no reason not to trial EZE and EZE should be an active comparator
- No LDL-C threshold barriers for EZE
- Company's NICE submission advisory board stated that EZE should be an active comparator
- EZE now available as a generic treatment – meaning its costs are low.

Responses from technical engagement

Company

- Still consider EZE part of standard care, not a comparator
- Provide feedback from interviews with 12 primary care physicians:
- All said EZE not used extensively in NHS:
 - Weak body of evidence
 - Patient resistance
 - 11/12 report <5% use
 - Not a mandatory treatment prior to PCSK9is
 - Lack of incentives to lower LDL-C in primary care
 - EZE more of a secondary care treatment
- EZE market share <3% in England since 2015, no reason to expect future increase
- CG181 includes EZE as a option, not a distinct step
- EZE usage in ORION trials higher than in NHS practice
- Company provide comparisons v EZE in subgroup populations (as requested)

NICE

Comparator company (Daiichi Sankyo)

- EZE should be an active comparator
 - in scope, now off-patent and cheaper than in TA385, included in NICE guideline 181
- EZE use increasing in UK. Prescription data (2021) suggest use in ~250,000 people
- EZE received by substantial % in ORION studies (25%-26% ORION-1, 50%-56% ORION-9, 10% ORION-10, 6%-7% ORION-11)

British Cardiovascular Society

- EZE should be considered as part of standard care and not a comparator
- EZE well-tolerated and cheap. Comparison of inclisiran v EZE would introduce an unnecessary step in access to inclisiran

Clinical experts (NICE)

- EZE normally considered part of SoC
- EZE more commonly used in secondary care
- Most people should be on statins + EZE (however, EZE use is low), inclisiran should be given after these treatments if LDL-C is too high

Primary Care Cardiovascular Society

- Treatment is statins (with EZE less often used, either as add-on or instead of statins)

Responses from technical engagement

HEART UK: The Cholesterol Charity

- EZE only effective if taken regularly. People do not have uniform access to EZE.
- Large variation in management of condition by GPs.
- Pathway not always completed (accounts for some variations in EZE prescribing).
- Inclisiran should be offered as an option in addition to EZE.

ERG comments after engagement

- EZE available at same treatment line (2nd line after MTS or 1st line statin intolerant).
- Company clinical expert survey indicates mixed interpretation of guidance for EZE use.
- Patient resistance/limited resources in primary care likely to affect all treatment options.
- Low uptake of EZE (company data) may be due to prior costs. Now available as generic, and increased cost-effectiveness may lead to more uptake.
- Inconsistent to consider EZE as part of standard care considering low uptake.
- NMA: █████% LDL-C reduction with EZE at a yearly drug cost per patient of £25.44.
- Acknowledge low EZE use, but there is widespread undertreatment of hypercholesteremia.
- ERG note ongoing projects to improve preventive treatments such as recent NICE Rapid Uptake Product (RUP) guidance for lipid management: may increase future EZE use.
- ERG maintains EZE is an active comparator and should not be absorbed into SoC.
- TA393 (Alirocumab), TA394 (evolocumab), TA694 (bempedoic acid) consider EZE a comparator.

NICE Should ezetimibe be considered as part of standard care (not a comparator) or as a comparator to inclisiran?

Additional issue 1: Generalisability of clinical trials results

Background

Clinical evidence for inclisiran comes from ORION 9, ORION 10 and ORION 11. The ERG note that no patients from the UK were enrolled in ORION 9 or ORION 10.

Company response after tech engagement

- Patient characteristics in ORION trials broadly comparable with CPRD study.

Clinical experts (NICE)

- Trial results are generalisable.

British Cardiovascular Society

- Trial results are generalisable.

ERG comments after tech engagement

- Disagree with company comment that ORION population broadly comparable to CPRD database.
 - However, forest plots show effectiveness of inclisiran does not vary across subgroups.
- Agree clinical trial evidence not generalisable to people with recent ASCVD event (within 3 months).

Comparator company after tech engagement (Amgen)

- ORION-10 and ORION-11 not generalisable to people with a recent ASCVD event: studies excluded people with a major cardiovascular event within past 3 months.
 - These people are at increased risk of subsequent ASCVD events.

Comparator company after tech engagement (Daiichi Sankyo)

- Trials did not include many people with statin intolerance: US ICER review concludes there is uncertainty in effectiveness of inclisiran in this population

British Cardiovascular Society

- Trial results generalisable to NHS practice.

Additional issue 3: analysis using Beliard (2018) for ASCVD HeFH

Background

Company use data from Mohrscladt 2004 for ASCVD HeFH population (due to CPRD study limitations in identifying HeFH). ERG notes Beliard 2018 may be a more appropriate source, but note this is also an issue in primary HeFH population (misclassification of HeFH).

Responses to tech engagement

Company

- Present analysis using Beliard 2018 for ASCVD HeFH.
- Not possible to include EZE as no data available to inform its efficacy in HeFH population.

Comparator company (Amgen)

- NICE should fully explore uncertainty relating to event rates

ERG comments after engagement

- Beliard 2018 more representative; larger sample size and more recent publication.
- Inclusion of EZE in ASCVD and PPER analysis increases ICER.

Baseline characteristics Mohrscladt v Beliard 2018 (ASCVD HeFH):

Study/Characteristics	Mohrscladt 2004	Beliard 2018
Age (Mean)	54	60
Gender (% male)	64%	72%
Number of participants	131	565
Years of follow up	1105	5779
CV rate for all events (per 1000 person years) (# of events)	143/1000 (158)	90/1000 (778)
Fatal CV event rates (per 1000 person years) (# of events)	12/1000 (13)	1.4/1000 (8)
Mean LDL-C (mmol/L)	7.27	3.72

Table 27 ERG report

Is using Beliard (2018) more appropriate for the ASCVD HeFH subgroup analysis ?

Additional issue 4: Impact of differences in CV risk and severity

Background

ERG does not agree with company assumption that differences in CV risk and severity within each subgroup population of interest (i.e., HeFH and ASCVD) would not impact relative efficacy (changes in LDL-C, HDL-C, and discontinuations).

Responses from technical engagement

Company

- [Redacted]
- [Redacted]

Clinical experts (NICE)

- ASCVD and HeFH not homogenous groups in terms of future risks but risks in both groups substantial.
- No evidence that increasing HDL cholesterol achieves clinical benefit

- Not an issue. LDL-C % reduction is constant. % reduction modestly lower in HeFH but absolute reductions greater (as LDL-C higher). Consistent benefit observed in primary/secondary prevention

Comparator company (Daiichi Sankyo)

- Statistically significant differences between subgroups for baseline LDL-C levels in ASCVD population.
- Should be considered: key model driver

ERG comments after tech engagement

- Limitation in evidence complicates any type of comparison for CV risk.
 - Inconsistent definitions may result in variability in distribution of CV risk across trials in NMA
- Agree baseline LDL-C (proxy for CV risk) [Redacted]

Additional issue raised during technical engagement (1): Company base case populations

Background

Company's 3 base case populations include a minimum LDL-C threshold of 2.6 mmol/L – however access to PCSK9 inhibitors is limited by different NICE recommended LDL-C thresholds

Company

- Provide analysis by PCSK9i thresholds recommendations

Comparator company (Daiichi Sankyo)

- For consistency with previous NICE appraisals, cost-effectiveness analysis should report by LDL-C thresholds

Comparator company (Amgen)

- Baseline LDL-C used in model not appropriate for cost-effectiveness analysis
 - Analysis should reflect populations eligible for PCSK9i treatments (LDL-C of 3.47 mmol/L appears too high for ASCVD population comparison)
 - Comparisons with EZE and no additional treatment should reflect the population not eligible for PCSK9is

ERG comments after tech engagement

- Concerned ICERs for ASCVD and PPER populations with LDL-C ≥ 2.6 mmol/L are obtained using mean LDL-C levels of 3.47 and 4.02 mmol/L, respectively.
- This is close to 3.5/4.0 mmol/L thresholds for which PCSK9is are available in ASCVD population. ERG provide analysis varying baseline LDL-C.

NICE

Are the company's base case analyses appropriate for comparisons with ALI/EVO and EZE/SoC?

Additional issue raised during technical engagement (2): Primary care setting and treatment pathway

Background

Company proposes inclisiran would be used in primary care.

Comparator company (Amgen)

- Assumption inclisiran initiated only in primary care does not reflect precedent with PCSK9is and inconsistent with NICE CG181.
- Feasibility of primary care use should be demonstrated: challenges of identifying appropriate populations and GP burden.
- Unlikely people at elevated risk would routinely start inclisiran in primary care.
- EVO can be self-administered after initiation in secondary care: less burdensome.
- Placing inclisiran before ALI/EVO means patients receive sub-optimal treatment.

British Cardiovascular Society

- Inclisiran can be used safely/effectively in primary care (where most relevant patients are managed). Lipid clinics are over-burdened.

Comparator company (Daiichi Sankyo)

- Important to clarify how inclisiran would be managed in primary care: route of administration, dosing, long half-life, and uncertain long-term safety.
- Clinical concerns: would primary care GPs feel comfortable giving inclisiran without significant additional training? May cause capacity issues, impacting other services.

Clinical expert (NICE)

- GPs may be reluctant to use in primary care for now: best to start in secondary care until shared care arrangement.
- Inclisiran requires nursing time but nothing more above what is already in place.

Clinical expert (NICE)

- Inclisiran should be used in primary and secondary care (Primary care use not difficult). Note: HeFH testing only available in secondary care.

NICE

Are there any issues surrounding inclisiran use in primary care/treatment pathway?

Additional issue raised during TE (3): Network Meta-analysis (NMA)

Background

Company undertook NMAs to compare inclisiran against comparator treatments.

Comparator company (Amgen)

- NMA estimates more favourable to inclisiran than co-primary endpoints: [REDACTED]
- [REDACTED] NMA timepoint likely influences results: SPC states max LDL-C reduction achieved at 150 days.
- Time-adjusted % LDL-C change (Day 90-540) more accurate estimate of efficacy (company scenario).
- QALY difference between SoC and inclisiran ([REDACTED]) appears [REDACTED] compared to TA393 (ALI v SoC: 0.40) and TA394 (EVO v SoC: 0.45)
- Counter-intuitive QALY difference: inclisiran v SoC; PPER population ([REDACTED]) and primary HeFH ([REDACTED])

Comparator company (Daiichi Sankyo)

- [REDACTED]
- Additional NMA with prior EZE use to match NICE scope where EZE does not control LDL-C should be provided.

ERG report comments

- [REDACTED] timepoint most commonly reported timepoint in NMA (scenario analysis present alternative timepoints).

Inclisiran efficacy estimates (trial endpoints and NMA)

	Published trial primary endpoint analyses (<i>Raal et al, 2020; Ray et al, 2020b</i>)		NMA base case model (% LDL-C change at [REDACTED])
	% LDL-C change at Day 510	Time-adjusted % LDL-C change (Day 90-540)	
ORION-10	-52.3% ^a	-53.8%	[REDACTED]% ^b
ORION-11	-49.9% ^a	-49.2%	[REDACTED]% ^b
Pooled ORION-10 and ORION-11	[REDACTED]% ^a	[REDACTED]%	[REDACTED]% ^b
ORION-9	-47.9% ^a	-44.3%	[REDACTED]% ^c

Clinical expert (NICE)

- Time averaged LDL-C reduction (peak and trough effect) between days 90-540 = likely results with twice yearly dosing from year 2

NICE ^a Multiple imputation washout model (prespecified primary analysis methodology)
^b Estimates for ASCVD MTD base case analysis
^c Estimate for HeFH MTD base case analysis

Additional issue raised during technical engagement (4): lack of long-term evidence

Background

Longer term data (>18 months) is not available for inclisiran. Company model therefore uses some assumptions on longer-term outcomes.

Comparator company (Amgen)

- Unlike PCSK9is, inclisiran lacks data on outcomes, long-term follow-up or real-world use.
- Inclisiran follow-up of 18 months, EVO up to 5 years + real-world data.
- Analysis exploring impact of inclisiran treatment waning is relevant (not provided).
- Assumption of immediate inclisiran benefit questionable: max LDL-C reduction at 150 days: for EVO usually 1-2 weeks. This should be explored. Speed of reduction particularly important for patients with recent ASCVD event.
- Lack of inclisiran discontinuation data: EVO easily managed with low discontinuation.
- Suggestion inclisiran leads to improved adherence untested. PCSK9i treatments can be conveniently administered at home.

Comparator company (Daiichi Sankyo)

- Main trial of inclisiran CV outcomes (ORION-4) includes only secondary prevention patients.
- No CV data for primary prevention anticipated; data validating outcomes in this population may not be available.

ERG report comments

- Given lack of longer term data, company could have provided a waning scenario.
- Notes that in TA393/TA394 no waning of treatment effect assumed.

NICE How appropriate are the company's assumptions due to lack of longer term evidence?

Translating changes in LDL-C to changes in risk

The driver of QALY gains in the model reflects the assumption that LDL-C reduction is associated with reduced risk of CVD events

- Currently, there are no outcome data on CVD events available from inclisiran clinical trials
 - ORION-4 due to report in 2026: data on CVD events (median follow-up 5 years)
- Reduced LDL-C levels assumed to reduce CVD events
- The company use an overall relative risk of 0.79 for major vascular events per 1 mmol/L reduction in LDL-C in the model (that is 21% less risk per 1mmol/l reported in CTT meta-analysis (2019); based on statins v control, median follow-up 4.9 years)
 - Example: Mean baseline LDL-C in ASCVD population in company submission is 3.47 mmol/l, applying NMA estimate of [REDACTED] reduces LDL-C by [REDACTED], to [REDACTED] associated with a risk reduction of [REDACTED] (based on RR 0.79)**
 - Previous CTT analyses (2010) reported absolute risk difference: -0.8% for 1.07mmol/L LDL-C reduction (3.6% v 2.8%)
- Estimated relative risks then applied to baseline risks (calculated using CPRD data)
- Longer term outcome trial data in ASCVD populations for PCSK9is have shown less favourable risk reductions compared to CTT analyses, although with shorter follow-up
 - Median follow-up was 2.8 years (ODYSSEY outcomes, alirocumab) and 2.2 years (FOURIER, evolocumab)

**calculation performed by NICE technical team CTT: Cholesterol treatment trialists

NICE How robust is the link between inclisiran's LDL-C lowering effect and future CVD events in the analyses?

Summary of cost-effectiveness analysis

Parameter	Description
Company base case	3 populations (with ezetimibe not considered a comparator) <ul style="list-style-type: none">• Secondary prevention population; ASCVD (including HeFH)• Primary prevention population; Elevated risk (PPER)• Primary prevention population; HeFH without ASCVD
Subgroup analyses	<ul style="list-style-type: none">• LDL-C levels• Statin intolerance• HeFH (ASCVD population only)
Sensitivity analyses	<ul style="list-style-type: none">• Parameter values varied by +/- 15% or use of 95% CI• PSA
Scenario analyses	<ul style="list-style-type: none">• Equal efficacy for inclisiran and PCSK9is• Time-adjusted LDL-C difference from ORION trials (90-540 days)• Including discontinuation rates for inclisiran, PCSK9is and statins• Inclisiran benefit starts from Day 90• CV risk ratio for 1st year from Collins et al• Using updated event costs from TA393• Including ezetimibe as a comparator: ASCVD and PPER populations
ERG analyses	Base case: same as company's but include ezetimibe as a comparator <ul style="list-style-type: none">• Additional analyses: use of THIN dataset (TA393) and LDL-C thresholds

Comparison with TA393* (Alirocumab)

Key comparisons of key modelling inputs between ID1647 (inclisiran) and TA393 (alirocumab)

Input/assumptions	TA393	ERG comments
Ezetimibe as part of standard of care (not a comparator)	Ezetimibe was the relevant comparator	Ezetimibe should be considered as a relevant comparator
Using CPRD data to inform baseline risks	Used THIN database to inform risks	CPRD database appropriate
Using CPRD to inform baseline group weighting	Used THIN database to inform weighting	CPRD weighting appropriate, scenario analysis using THIN weighting provided
Use ORION trial to inform baseline LDL-C levels	THIN database to inform baseline LDL-C levels	ORION trial LDL-C values appropriate
Use of updated CTT meta-analyses for translating changes in LDL-C to changes in risk	Used CTT meta-analyses to inform changes in risk	CTT analysis appropriate

Cost-effectiveness results, deterministic (1)

Secondary prevention population; ASCVD (including HeFH) with LDL-C ≥ 2.6 mmol/L despite maximally tolerated statins [mean baseline LDL-C = 3.47 mmol/L]

Company base case (v SoC)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC					
Inclisiran+SoC					
Alirocumab+SoC					
Evolocumab+SoC					

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

ERG base case (includes EZE)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Ezetimibe+SoC	*****	*****	*****	*****	*****
SoC	*****	*****	*****	*****	*****
Inclisiran+SoC	*****	*****	*****	*****	*****
Alirocumab+SoC	*****	*****	*****	*****	*****
Evolocumab+SoC	*****	*****	*****	*****	*****

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

Cost-effectiveness results, deterministic (2)

Primary prevention population; elevated risk (PPER*) with LDL-C ≥ 2.6 mmol/L despite maximally tolerated statins [mean baseline LDL-C = 4.02 mmol/L]

Company base case (v SoC)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	██████████	██████████	██████████	██████████	██████████
Inclisiran+SoC	██████████	██████████	██████████	██████████	██████████
Alirocumab+SoC	██████████	██████████	██████████	██████████	██████████
Evolocumab+SoC	██████████	██████████	██████████	██████████	██████████

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

ERG base case (includes EZE)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Ezetimibe+SoC	██████████	██████████	██████████	██████████	██████████
SoC	██████████	██████████	██████████	██████████	██████████
Inclisiran+SoC	██████████	██████████	██████████	██████████	██████████
Alirocumab+SoC	██████████	██████████	██████████	██████████	██████████
Evolocumab+SoC	██████████	██████████	██████████	██████████	██████████

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

Cost-effectiveness results deterministic (3)

Primary prevention population; HeFH without ASCVD with LDL-C ≥ 2.6 mmol/L despite maximally tolerated statins [mean baseline LDL-C = 4.09 mmol/L]

Company base case (v SoC)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC					
Inclisiran+SoC					
Alirocumab+SoC					
Evolocumab+SoC					

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

ERG base case – Not possible to include a comparison with ezetimibe in HeFH populations. ERG notes that ICER for the comparison of inclisiran with ezetimibe would be higher than the ICER for the comparison with SoC. *****

Innovation and equalities

Innovation

- Company: first cholesterol-lowering siRNA and potential to change how LDL-C lowering is managed
- May improve adherence with twice yearly administration compared to PCSK9i treatment which require more frequent dosing
- NICE clinical experts: “game changer”, allows a far wider and greater reduction in LDL-C levels. A “sea change” in ability to reduce cholesterol in high risk populations

Equalities

- Cardiovascular disease strongly associated with health inequalities and greatest cause of premature mortality in areas of deprivation
- Company: delivery of inclisiran in primary care would help address low uptake of treatments and improve healthcare provision
 - Company believe improved equality of access to effective treatment represents a benefit that is not captured in the QALY
- HEART UK also raise a number of potential equality issues in their submission