NICE National Institute for Health and Care Excellence

Slides for public observers

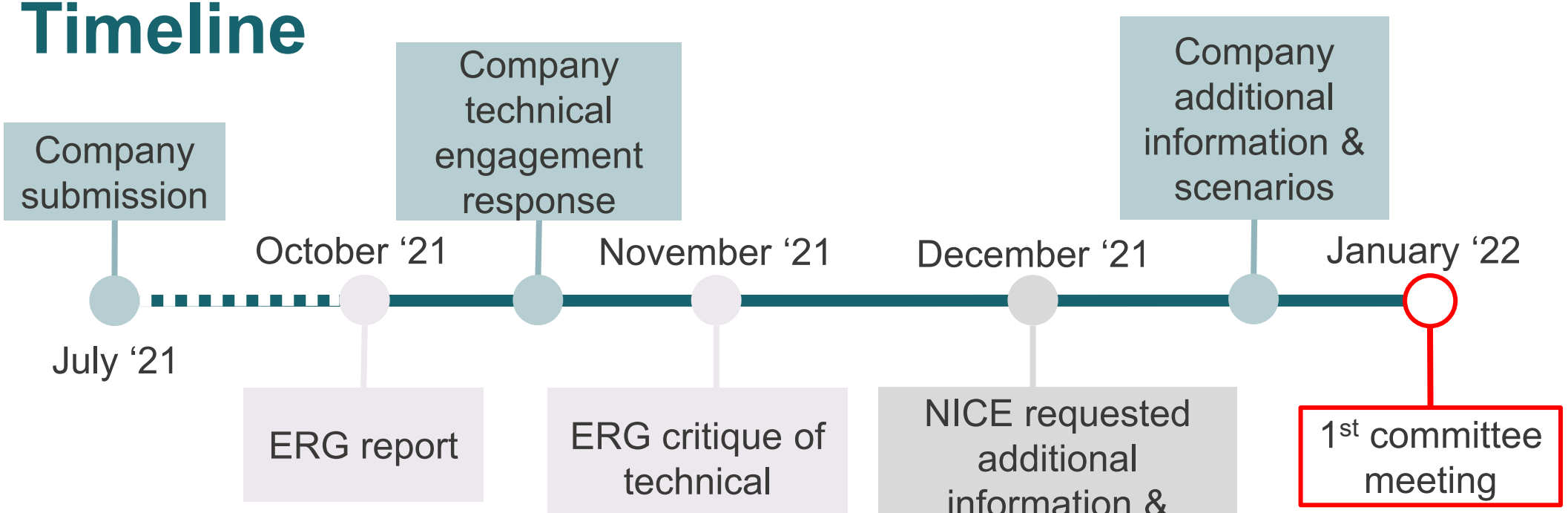
Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides

Lead team presentation

Lead team: Rob Forsyth, Subhash Pokhrel, Stella O'Brien
ERG: Kleijnen Systematic Reviews
Technical team: Steve O'Brien, Catie Parker, Alex Filby, Ross Dent
Company: Amarin

11 January 2022

Timeline



Did not update base case:
- Concerns with time to event analysis

- Updated time to event analysis

Scenarios:
- Time to treatment discontinuation
- Treatment waning
- Treatment independent non-CV related death hazard ratios

Company
ERG
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Note: Due to time constraints, company's additional information & scenarios not fully validated by ERG

CV, cardiovascular; ERG, evidence review group; TSD, technical support document

Disease background

CVD

A group of conditions often related to narrowing of arteries. Cardiovascular events include **myocardial infarction** and **stroke**

Epidemiology

In England, around **6.4 million** people are living with CVD[1]

Estimated **25%** to **35%** of people on statins have elevated triglycerides

Mortality

In England, **1** in **4** deaths is caused by CVD[2]

In 2020, **137,152** people died from CVD in England[1]

Risk factors

Age, hypertension, dyslipidaemia (**high LDL, TGs, cholesterol**), diabetes, physical inactivity, and obesity

CVD, cardiovascular disease; LDL, low-density lipoproteins; TG, triglyceride

1. British Heart Foundation 2021, 2. Public Health England 2019

Perspectives on managing CVD risk factors

- Many premature and preventable deaths (approx. 26%)
- Access to NHS Health Checks varies across the country
  - In 2020, 97% of NHS Health Checks were cancelled
- Current treatment options
  - Non-pharmaceutical interventions (NPIs) for modifiable risk factors; e.g., BMI, food choices, exercise, alcohol consumption, tobacco cessation
  - Pharmaceutical interventions (PIs). Statins are the backbone. Fibrates prescribed for some but another treatment option is helpful
- Adherence to NPIs and statin therapy can be poor
  - Lack of data on efficiency and effectiveness of NPIs
  - 75% of people stop taking lipid lowering therapies after 2 years
- Barriers to access
  - No more barriers should be introduced that delay risk reduction

BMI, body mass index

Equality and equity considerations

- People with Black, Asian and minority ethnic family backgrounds have higher triglyceride levels and increased CVD risk factors
- People in England's most deprived areas are almost 4 times more likely to die prematurely from CVD than people in the least deprived areas
- Variation in access to secondary and tertiary care
- People with severe mental illness are more likely to develop and die from preventable conditions like CVD
- People with learning disabilities are at increased risk of developing CVD
- Some faiths and ethical beliefs may restrict use of fish products
- Pregnancy and breast-feeding

CVD, cardiovascular disease

Clinical expert perspective

Current care

- **Unmet need** for people with raised TGs with residual risk of CVD events even when optimally treated
- **No effective treatment** to add to statins for residual raised TGs which may reflect apoB
- Prevalence of people with co-existing raised TGs and CVD risk is increasing

Icosapent ethyl

- Expect it to **improve quality of life**
- Expect most benefit in **secondary prevention**
- Benefit in practice may be less than trial
- **Adverse event concerns**: atrial fibrillation, bleeding, constipation
- Mechanism of action seems independent of lipid modulation

Considerations for implementation

- If it's recommended, would need to implement a full **fasting lipid profile**
- Expect it to be used mostly in **primary care** but also in **secondary care**
- Some GPs are overwhelmed by CVD guidance & pushback about value of managing lipids

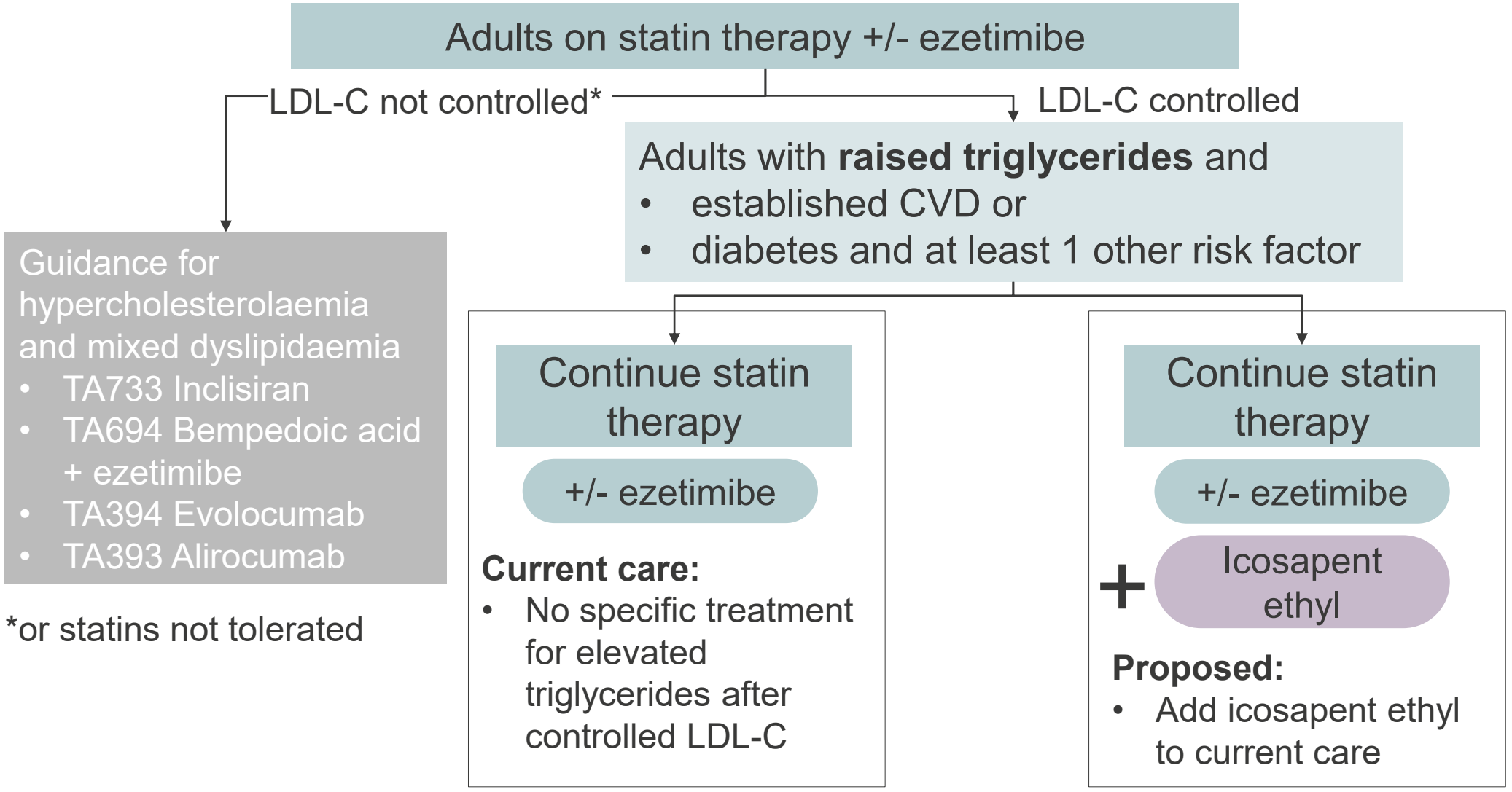
apoB, apolipoprotein B; CVD, cardiovascular disease; TG, triglyceride

Icosapent ethyl (Vazkepa, Amarin)

Marketing authorisation (MHRA)	Indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL [≥ 1.7 mmol/L]) and • established cardiovascular disease, or • diabetes, and at least one other cardiovascular risk factor. Risk factors from SPC: – hypertension or on an antihypertensive medicinal product – age at least 55 years (men) or at least 65 years (women) – low high-density lipoprotein cholesterol levels – smoking – raised high-sensitivity C-reactive protein levels – renal impairment – micro or macroalbuminuria – retinopathy – reduced ankle brachial index
Mechanism of action	Not fully understood, but appears to modulate atherosclerosis pathway by lipid and non-lipid effects
Administration	Oral
Price	Anticipated list price £173 per pack of 120 capsules (£2,106.28 per year). No Patient Access Scheme

dL, decilitre; L, litre; mg, milligram; MHRA, Medicines and Healthcare products Regulatory Agency; mmol, millimole; SPC, summary of product characteristics

Treatment pathway & proposed position



- Controlled LDL-C levels (REDUCE-IT): > 1.04 mmol/L and ≤ 2.60 mmol/L
- Raised triglycerides (marketing authorisation): ≥ 1.70 mmol/L

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre

Key issues (1/2)

Model driver | Unknown impact | Small impact

	Issue description	Questions	Impact
1	REDUCE-IT population narrower than scope	Can recommendations be made in line with full marketing authorisation?	
3	MACE composite outcome	Is the composite 5-point MACE outcome appropriate to use in the model?	
4	REDUCE-IT generalisability	Are the results from REDUCE-IT generalisable to the NHS in England?	
5	Model structure	Is the company's partitioned survival model appropriate for decision making?	N/A
6	Using partial KM	Is the company's updated time to event analysis acceptable?	
7	Time to event analysis		
8	DSU guidance not followed		
9	Assumption of no treatment waning	Is a 10 year, 20 year, or no waning assumption most appropriate?	

Partially resolved/for brief discussion | Unresolved, for discussion

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DSU, Decision Support Unit; KM, Kaplan-Meier; MACE, major adverse cardiovascular event

Key issues (2/2)

Model driver Unknown impact Small impact

	Issue description	Question	Impact
10	Treatment-dependent non-cardiovascular related death hazard ratios	Should non-cardiovascular related death hazard ratios be treatment dependent or independent?	
13	Time to treatment discontinuation	Which curve is most appropriate for time to treatment discontinuation?	

Unresolved, for discussion

Issues resolved at technical engagement

Model driver | Unknown impact | Small impact

	Issue	Technical engagement	Impact
2	Time to determine stable statin dose	Time to determine stable dose of statins in REDUCE-IT likely similar to clinical practice, around 3 months	
11	Utility values	ERG agrees that Stevanovic & O'Reilly baseline values and CG181 multipliers are likely appropriate	
12, 14	Event costs not adjusted for time since previous event	Company updated event costs to reflect cost per day after event instead of one-off event cost. ERG satisfied with company's changes	
15	Model validation	Company provided validation checklists: AdViSHE and TECH-VER. ERG satisfied with model validation	

Resolved

Summary

Comparators	Best supportive care = stable dose of statins with or without ezetimibe
Subgroups	• **Secondary prevention** (CV1): Adults with established cardiovascular disease • **Primary prevention** (CV2): Adults with diabetes and at least 1 other risk factor (slide 7)
REDUCE-IT clinical trial	Randomised controlled trial comparing icosapent ethyl with placebo (mineral oil)
Model	Partitioned survival model with 8 health states

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

REDUCE-IT overview

Randomised, double-blind, placebo-controlled phase 3 trial

Population

N=8,179: No UK participants
General inclusion criteria:

- **TG** ≥1.53 mmol/L* and <5.64 mmol/L
- **LDL-C** >1.04 mmol/L and ≤2.60 mmol/L
- Stable dose of **statins** with or without ezetimibe

Primary prevention (29%)

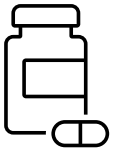
- Adults 50 or older
- Diabetes mellitus
- At least 1 other cardiovascular risk factor†

Secondary prevention (71%)

- Adults 45 or older
- Established CVD

Treatment

Icosapent ethyl
(4g per day)
n=4,089



Placebo
(mineral oil)
n=4,090

Endpoint

Primary: Time from randomisation to first occurrence of 5-point MACE:

- Cardiovascular (CV) death
- Nonfatal myocardial infarction (MI)
- Nonfatal stroke
- Coronary revascularisation
- Unstable angina

Secondary: Time from randomisation to first occurrence of composite of CV death, nonfatal MI, or nonfatal stroke

Median follow up: 4.9 years

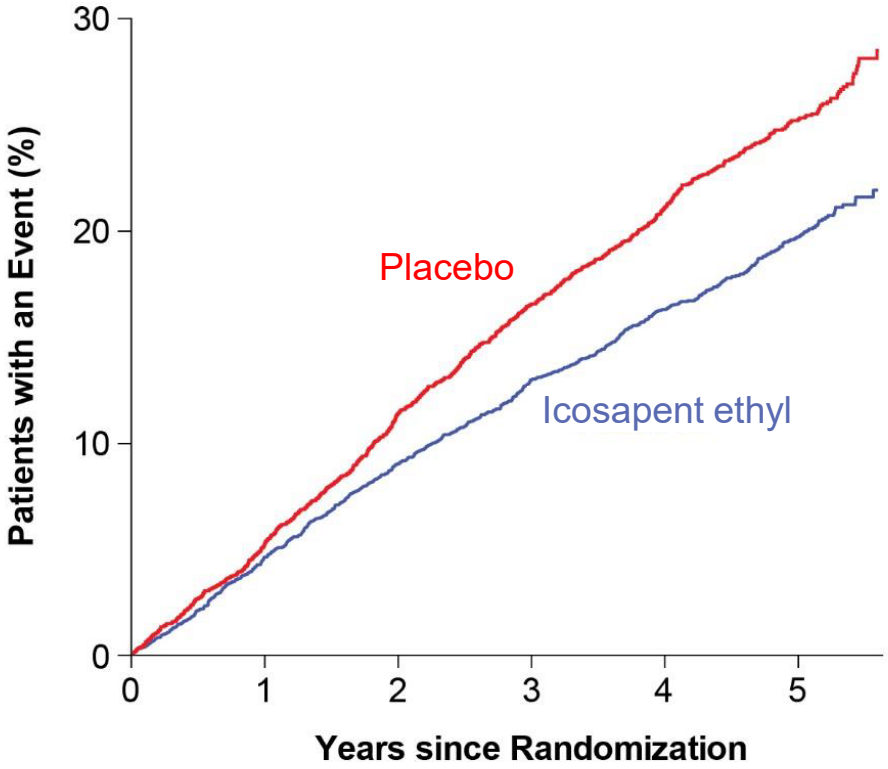
*10% variability (1.69 mmol/L) & in 2013 changed to ≥ 2.26 mmol/L, †including older age, cigarette smoking, hypertension, HDL-C ≤1.04 mmol/L, renal disfunction (full list, slide 7)

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; mmol/L, millimoles per litre; TG, triglyceride

REDUCE-IT results, intention to treat population

Randomised, double-blind, placebo-controlled phase 3 trial

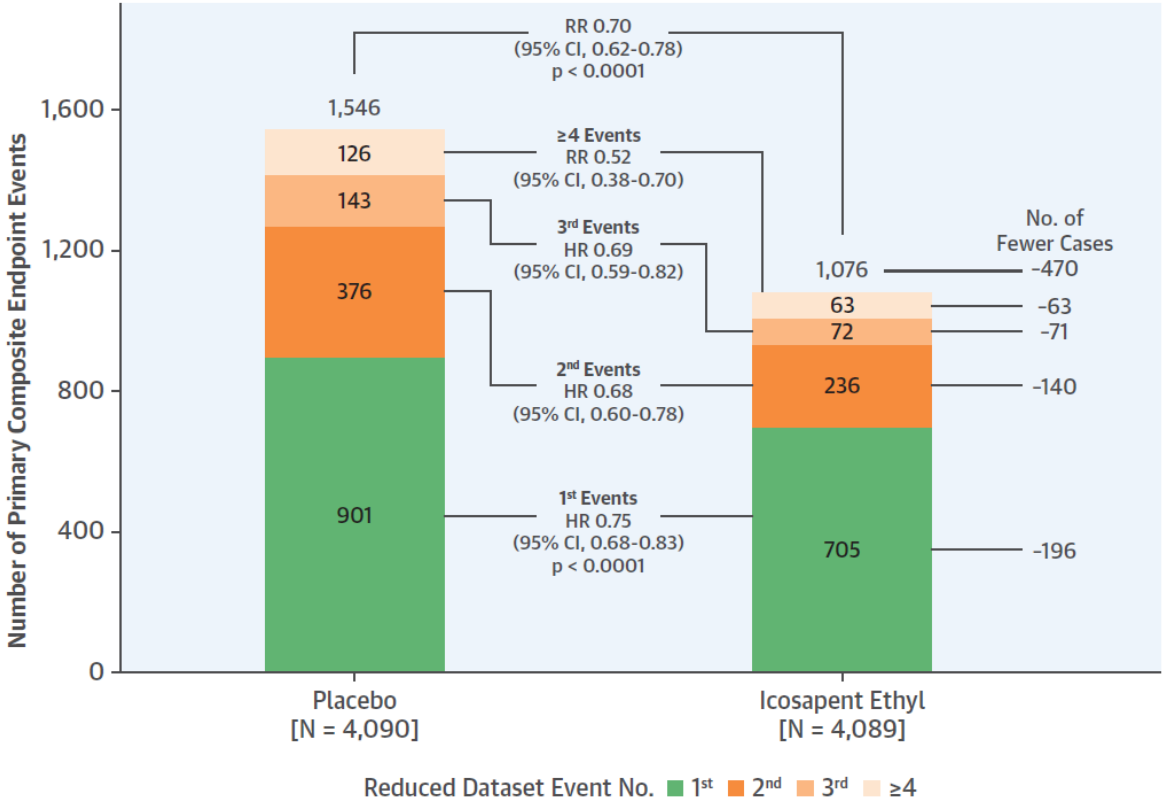
Kaplan-Meier curves for 5-point MACE composite endpoint



No. at Risk

Placebo	4090	3743	3327	2807	2347	1358
Icosapent ethyl	4089	3787	3431	2951	2503	1430

Graphical representation of total events in primary endpoint



Bhatt, D.L. et al. J Am Coll Cardiol. 2019;73(22):2791-802.

Excludes subsequent events on the same day

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HR, hazard ratio; MACE, major adverse cardiovascular event; RR, relative risk

REDUCE-IT results, subgroups

Secondary prevention

Primary prevention

1st event 2nd event 3rd event 4th event

CI, confidence interval; HR, hazard ratio; RR, relative risk

REDUCE-IT: comments on trial (1/2)

Professional organisation

- Level of risk reduction is disproportionate to triglyceride lowering
- Mineral oil not neutral, increases inflammatory markers. Prefer corn oil
- In STRENGTH analysis, EPA relative risk reduction half benefit seen in REDUCE-IT

ERG response

- Icosapent ethyl is not the same as EPA
- Takahito et al. 2021 may indicate REDUCE-IT results overestimate benefit, but
  - Plausible that corn oil reduces risk of MACE and analysis was based on oil surrogate
  - No significant effect of 2 of the surrogates (LDL-C or C-reactive protein) on primary outcome in REDUCE-IT
- 2020 systematic review found mineral oil 'does not meaningfully affect study conclusions when used as a placebo at the quantities used in clinical trials'
  - But, study not well reported & co-author employed by Amarin

European Public Assessment Report (EPAR)

- Based on analyses provided by company, a putative negative effect of mineral oil should not account for more than 0.3 – 3% of MACE events
- Assuming unlikely worst-case scenario, the remaining beneficial effect of icosapent ethyl on MACE events can be considered robust and meaningful

EPA, eicosapentaenoic acid; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event

REDUCE-IT: comments on trial (2/2)

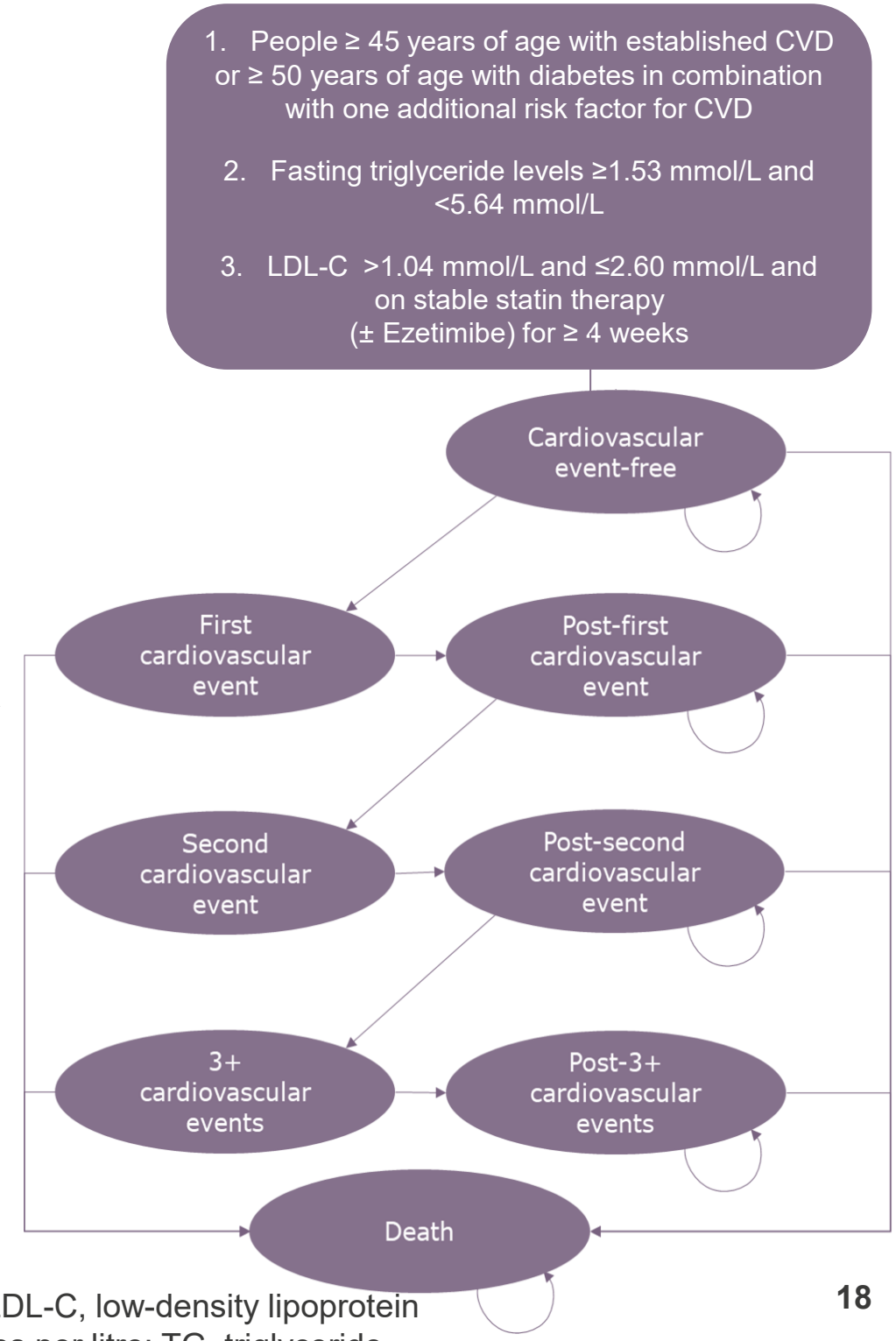
NHS England

- REDUCE-IT: findings different from previous studies of omega-3 fatty acids & magnitude of benefit much greater than predicted based on change in triglyceride levels
- REDUCE-IT authors note ASCVD benefits not explained by change in triglycerides or atherogenic and inflammatory biomarkers. Cardiovascular benefit may be driven by pleiotropic effects of EPA
- STRENGTH trial: In population at high risk of, or with established ASCVD, 4g/day EPA-75% and DHA-25% compared with corn oil for 3.5 years had no beneficial effect on ASCVD risk
- Danish investigators found contrasting results of ASCVD prevention in REDUCE-IT and STRENGTH trials could be partly explained by differences in effect of active and comparator oils on lipid traits and C-reactive protein. Negative effect of mineral oil in REDUCE-IT increased predicted ASCVD risk by 7%
  - NHSE considers treatment effect in REDUCE-IT likely overestimated
  - Expect company to provide a scenario with magnitude of treatment effect reduced by 7% to account for estimated increased risk of ASCVD events associated with mineral oil use

ASCVD, atherosclerotic cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; NHSE, NHS England

Company's model

- Health state cohort model (partitioned survival approach)
- 8 health states based on occurrence of cardiovascular events and death
- 1 day cycle length, 36 year horizon
- Mean age at baseline: 64 years
- Percent male at baseline: 71%
- REDUCE-IT used to estimate parametric survival models for health state occupancy
  - Estimated using composite end points and subdivided between event types
    - Cardiovascular death
    - Myocardial infarction
    - Stroke
    - Unstable angina
    - Revascularisation



CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre; TG, triglyceride

Issue 1: Eligible population

Summary: Marketing authorisation does not specify **age** or **LDL-C level**

REDUCE-IT included people:

- **≥ 45yrs** with CVD
- **≥ 50yrs** with diabetes and at least 1 other risk factor

REDUCE-IT included people with:

- LDL-C >1.04mmol/L and ≤ 2.60mmol/L

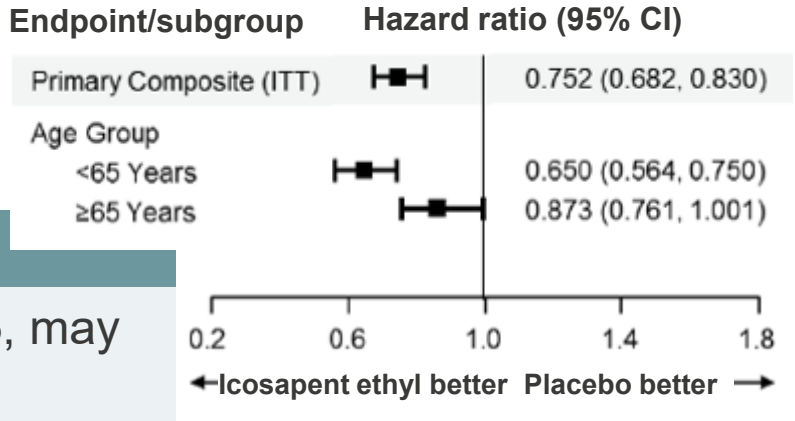
Marketing authorisation:
"to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL [≥ 1.7 mmol/l]) and established cardiovascular disease, or diabetes, and at least one other cardiovascular risk factor"

Company TE response

Population should follow REDUCE-IT, which is narrower than licensed indication

ERG

Subgroup analysis indicates age might have substantial effect on outcome



Clinical expert comments

- No biological reason to restrict drug to people over 45, may disadvantage people at risk
- Some people in NHS < 45 with CVD or diabetes and raised triglycerides especially in people with South Asian family backgrounds

? Can recommendations be made in line with full marketing authorisation?

CI, confidence interval; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre; yrs, years

Issue 3: Composite MACE outcome

Background

- REDUCE-IT had composite 5-point MACE
- **ERG**: composite outcomes may mask treatment effect of individual outcomes. Should explore impact of single outcomes

Company TE response

- Composite 5-point MACE used to model time of a 1st, 2nd or 3rd+ event
- Distribution of specific cardiovascular events experienced by patients in each treatment group was applied (table)
- Using single outcomes would not lead to large increase in ICER

ERG

Company has not explored impact of single outcomes so ERG view remains the same

Clinical expert comments

Most major trials use composite MACE

Distribution of events from REDUCE-IT

		Icosapent ethyl	Placebo
1st event	CV death	[redacted]	[redacted]
	MI	[redacted]	[redacted]
	Stroke	[redacted]	[redacted]
	Unstable angina	[redacted]	[redacted]
	Revascularisation	[redacted]	[redacted]
	Total	705	901
2nd event	CV death	[redacted]	[redacted]
	MI	[redacted]	[redacted]
	Stroke	[redacted]	[redacted]
	Unstable angina	[redacted]	[redacted]
	Revascularisation	[redacted]	[redacted]
	Total	236	376
3rd event	CV death	[redacted]	[redacted]
	MI	[redacted]	[redacted]
	Stroke	[redacted]	[redacted]
	Unstable angina	[redacted]	[redacted]
	Revascularisation	[redacted]	[redacted]
	Total	[redacted]	[redacted]

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? Is the composite 5-point MACE outcome appropriate to use in the model?

CV, cardiovascular; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction

Issue 4: REDUCE-IT generalisability (1/2)

Background

REDUCE-IT did not include any UK participants

Company

Provided baseline comparison of primary and secondary prevention subgroups with Steen et al.

- Steen et al. was retrospective, cross-sectional analysis of 183,565 people in the UK – from The Health Improvement Network (THIN) database
- See slide 37

ERG

- Differences in characteristics that may affect treatment between REDUCE-IT and Steen
- Unclear if Steen et al. is relevant to UK clinical practice, it is 5 years old
- Patients in UK clinical practice for whom the company submission would be most appropriate would be those who most resemble patients in REDUCE-IT
  - e.g. with diabetes in the primary prevention population and with hypertension in both populations

Clinical experts

- Uncertain generalisability: trial does not represent ethnic groups in the UK who have higher triglycerides and may have benefited more
- Current UK practice does not routinely assess triglycerides or set an LDL target, so the eligible population would not be easily identifiable

LDL, low-density lipoprotein

Issue 4: REDUCE-IT generalisability (2/2)

NHS England

Generalisability in relation to current management of high-risk ASCVD

- In REDUCE-IT, only 6.4% had ezetimibe & <4% had PCSK-9 inhibitors. These each reduce triglycerides by 5-10% beyond statin effect
- Inclisiran recommended for people with LDL-C >2.6 mmol/L despite maximum tolerated statin, with or without ezetimibe. Similar population to REDUCE-IT

→ Combination of therapies could reduce triglycerides below threshold for icosapent ethyl & benefit of icosapent ethyl for people having these treatments unknown

Generalisability in relation to current management of type 2 diabetes mellitus

- People are offered lifestyle advice which can decrease triglycerides
- Poor blood glucose control associated with hypertriglyceridemia and should be optimised
- Recently updated NICE guidance recommends earlier use of SGLT2 inhibitors for people with diabetes & high ASCVD risk. CV risk protection from SGLT2 inhibitors not fully appreciated in REDUCE-IT, uncertain how many people in REDUCE-IT had SGLT2 inhibitors or GLP-1 agonists

→ These treatments could reduce triglycerides below threshold for icosapent ethyl & benefit of icosapent ethyl for people having these treatments unknown

? Are the results from REDUCE-IT generalisable to the NHS in England?

ASCVD; atherosclerotic cardiovascular disease; CV, cardiovascular; GLP-1, glucagon-like peptide-1; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre; PCSK-9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium-glucose cotransporter-2

Issue 5: Model structure (1/2)

ERG comments before TE

- Unclear appropriateness of partitioned survival model, assumes independence of endpoints
- Model different than related topics: TA393, TA394, TA420
  - Structure does not explicitly model non-fatal CV events but uses composite endpoint
  - 1 day cycle may make model error prone
  - Event costs modelled to last 1 day, but utilities applied 60 days post event (likely over estimated costs)
- Prefer individual patient level simulation

ERG post technical engagement

- Requested company provide detailed comparison of its model with validation model (slides 38-39)
- Due to time constraints, not fully reviewed validation and detailed comparison

Company

- Provided state transition model for validation (structure, next slide)
- Model comparison shows similar clinical estimates (slide 40)
  - shows company's model is appropriate
  - proportion of patients alive lower in company model because non-CV related mortality HR used to account for additional risk of death following CV event – not in validation model
- Updated event costs as daily cost for 60 days

Comparison of selected clinical estimates: company and validation models at 30 years

	Model	Icosapent ethyl	BSC
2nd event	Validation	[redacted]	[redacted]
	Company	[redacted]	[redacted]
3rd event	Validation	[redacted]	[redacted]
	Company	[redacted]	[redacted]
Patients alive	Validation	[redacted]	[redacted]
	Company	[redacted]	[redacted]

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BSC, best supportive care; CV, cardiovascular; TE, technical engagement

Issue 5: Model structure (2/2)

Validation state-transition model structure

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

Company and validation model results

Population	Model	ICER (£/QALY)
ITT	Validation	[redacted]
	Company	28,266
Primary prevention	Validation	[redacted]
	Company	85,438
Secondary prevention	Validation	[redacted]
	Company	22,796

[redacted]

? Is the company's partitioned survival model appropriate for decision making?

AF, atrial fibrillation; CR, coronary revascularisation; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; MI, myocardial infarction; QALY, quality-adjusted life year; VT, ventricular tachycardia

Issues 6, 7 & 8: Time to event analysis (1/3)

ERG comments before TE

- Observations when only 10% at risk removed
- Uncertainty around long term survival curves
- Company did not follow TSD 14
- Requested: fitted models, selection justification, and alternative to literature HR approach

Company

Updated base case following TSD 14:

- Complete Kaplan Meier
- Fitted parametric models* to REDUCE-IT 1st, 2nd, 3rd+ event, with treatment as covariate
- Proportional hazards assumption holds (ERG agrees, slides 41-42)
- Log-cumulative hazard plot, visual inspection, AIC/BIC, & compared with validation model

Parametric models fitted to **1st event**: ITT population, placebo

[redacted]

Parametric models fitted to **1st event**: ITT population, icosapent ethyl

[redacted]

*Unable to fit Weibull as it caused error

Note: Updated analyses not fully validated by ERG

AIC, Akaike information criterion; BIC, Bayesian information criterionHR, hazard ratio; ITT, intention to treat; TE, technical engagement; TSD, technical support document

Issues 6, 7 & 8: Time to event analysis (2/3)

Company

- Uncertainty around 2nd and 3rd+ event distributions
- Log-logistic best fitting statistically (base case)
- Exponential estimates closer to validation model
- Different distributions have small impact on ICER (slide 35)

Note: Analyses not fully validated by ERG

[redacted]

ICER, incremental cost-effectiveness ratio; ITT, intention to treat

? Is the company's updated time to event analysis acceptable?

Issues 6, 7 & 8: Time to event analysis (3/3)

Extrapolated proportion of people experiencing 1st event, exponential

	1 year	5 years	10 years	20 years	30 years
Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Extrapolated proportion of people experiencing 2nd event

		1 year	5 years	10 years	20 years	30 years
1	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Extrapolated proportion of people experiencing 3rd + event

		1 year	5 years	10 years	20 years	30 years
1	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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1 log-logistic (company's base case for 2nd & 3rd + events)

2 exponential (estimates closer to validation model)

Note: Analyses not fully validated by ERG

Issue 9: Treatment waning

Company

- Base case **no** treatment waning, provided scenarios with 10 or 20 year waning assumptions
- No waning in similar appraisals: TA393, TA394 & TA733
- Analysis of REDUCE-IT shows no treatment waning during trial across all populations (below)

[redacted]

Recent appraisals

- **TA733 inclisiran**: Assumption of no waning of treatment effect may be appropriate but adds uncertainty
- **TA694 bempedoic acid + ezetimibe**: Company assumed effect maintained for model duration or until treatment stopped. ERG noted there may be slight waning. Committee concluded there is uncertainty in the evidence

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? Is a 10 year, 20 year, or no waning assumption most appropriate?

ERG

- Base case: waning 10 years post trial completion
- **Remaining uncertainty**
- Want to see smoothed hazard plots over time per arm and for subgroups

Clinical experts

- Limited data for long term treatment effect
- Assumption of no treatment waning reasonable

Issue 10: Treatment-dependent non-cardiovascular related death hazard ratios

Company

- Base case: treatment specific non-cardiovascular related death hazard ratios
- Do not agree with ERG approach of applying average of treatment dependent hazard ratios per health state to both treatment groups (subgroup analysis)
  - Primary and secondary prevention not comparable
  - Diabetes and number of prior events identified as non-cardiovascular related mortality modifiers so cannot be ignored
- Scenario applying treatment-independent hazard ratios, but used distribution of events that occurred across both treatment arms

Event	Treatment independent HR	Icosapent ethyl HR	Placebo HR
None	1.54	1.54	1.54
1st	2.12	2.12	2.12
Post 1st	2.12	2.12	2.12
2nd	2.36	2.27	2.45
Post 2nd	2.36	2.27	2.45
3rd	2.58	2.56	2.60
Post 3rd	2.58	2.56	2.60

ERG

- Agree non-cardiovascular related death hazard ratios should be calculated separately for CV1 and CV2 subgroups
- Would like to see evidence that diabetes and number of events are non-cardiovascular related mortality modifiers

? Should non-cardiovascular related death hazard ratios be treatment dependent or independent?

HR, hazard ratio

Issue 13: Extrapolation of time to treatment discontinuation

38 year extrapolation of TTD based on icosapent ethyl discontinuation in REDUCE-IT

ERG

- Weibull, Gompertz, log-logistic & log-normal all second-best fit
- Base case: log-logistic
- Uncertain without long term data

Clinical experts

- Most CVD drugs have long-term adherence around 60% (Wei et al. 2008)
- Discontinuation may be greater in primary prevention group

? Which curve is most appropriate for time to treatment discontinuation?

CVD, cardiovascular disease; TTD, time to treatment discontinuation

Other considerations

Innovation

- Clinical experts: Innovative because it appears to work on a pathway that is not yet defined and addresses unmet need of people with elevated triglycerides and residual CVD risk

Equality issues

- People with Black, Asian and minority ethnic family backgrounds have higher triglyceride levels
- People in England's most deprived areas are almost 4 times more likely to die prematurely from CVD than people in the least deprived areas
- People with severe mental illness are more likely to develop and die from preventable conditions like CVD
- People with learning disabilities are at increased risk of developing CVD
- Some religions have restrictions on fish products

? Are there any equalities issues that need to be taken into account?

CVD, cardiovascular disease

Base case assumptions

ERG analyses **not** updated at technical engagement due to concerns with model and survival analysis

		Company old base case	ERG (dependent on company old base case)	Company new base case
6	**KM data**	Reduced dataset (excluded observations after 10% at risk)	Reduced dataset (*noted complete dataset should be used*)	Complete KM
7,8	**Extrapolated time to event curves**	Separate curves fit to REDUCE-IT treatment arms	Separate curves for treatment arms (*noted company did not follow TSD 14*)	Per TSD 14, fitted parametric models to data with treatment group as covariate
9	**Treatment waning**	No waning	10 years post trial	No waning
10	**Non-CV related death HR**	Treatment dependent	Treatment independent	Treatment dependent
12, 14	**Event costs**	Applied as one off costs	Applied as one off costs, corrected (*noted daily cost more appropriate*)	Applied as daily cost for 60 days post event
13	**Time to treatment discontinuation**	Exponential	Log-logistic	Exponential

Note: Updated time to event analysis not fully validated by ERG

NICE

HR, hazard ratio; KM, Kaplan-Meier; TE, technical engagement; TSD, Technical Support Document

Summary of cost-effectiveness results

Whole population, secondary prevention & primary prevention

Company's deterministic base case results

Population	Incremental costs	Incremental QALYs	ICER (£/QALY)
Intention to treat	£10,632	0.376	28,266
Secondary prevention (CV1)	£10,534	0.462	22,796
Primary prevention (CV2)	£11,276	0.132	85,438

ERG's deterministic base case results before technical engagement

Population	ICER (£/QALY)
Intention to treat	122,598
Secondary prevention (CV1)	88,888
Primary prevention (CV2)	758,717

- ERG results use old time to event analysis – separate curves for treatment arms
- Due to time limitations, unable to present ERG results with updated time to event analysis

Note: Company's results not fully validated by ERG

NICE

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Deterministic cost-effectiveness results (1/2)

Secondary prevention (CV1)

		Incremental cost	Incremental QALYs	ICER (£/QALY)
1	Company base case	£10,534	0.462	**22,796***
2	Log-logistic for time to treatment discontinuation (1+2)	£11,642	0.462	25,193
3	10-year post trial treatment waning applied to 3rd + events (1+3)	£11,078	0.409	27,086
4	Combined scenario (1+2+3+4)	£12,170	0.409	29,756

*Probabilistic: £22,075/QALY

Additional scenarios

5	20-year post trial treatment waning applied to 3rd + events (4+5)	£12,034	0.423	28,455
6	Treatment independent non-CV related death hazard ratios (4+6)	£12,102	0.389	31,121

Note: Results not fully validated by ERG

NICE

CV, cardiovascular; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Deterministic cost-effectiveness results (2/2)

Secondary prevention (CV1)

Time to event scenarios based on combined scenario 4 (previous slide)

	Distribution	Incremental cost	Incremental QALYs	ICER (£/QALY)
1st event	**Exponential (company base case)**	**£12,170**	**0.409**	**29,756**
	Gompertz	£12,198	0.413	29,547
	Log-logistic	£12,392	0.380	32,582
	Lognormal	£12,587	0.361	34,821
	Generalised gamma	£12,286	0.397	30,976
2nd event	Exponential	£12,052	0.429	28,090
	Gompertz	£12,361	0.404	30,623
	Log-logistic (company base case)	**£12,170**	**0.409**	**29,756**
	Lognormal	£12,050	0.389	30,984
	Generalised gamma	£12,201	0.416	29,357
3rd + event	Exponential	£12,621	0.390	32,353
	Gompertz	£11,567	0.448	25,797
	Log-logistic (company base case)	**£12,170**	**0.409**	**29,756**
	Lognormal	£12,575	0.384	32,739

Unable to provide results using Weibull for any event & generalised gamma for 3rd + events as they resulted in errors

Note: Scenarios not fully validated by ERG

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year