NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Appraisal Consultation Document (ACD)** as issued to consultees and commentators

2. **Comments on the Appraisal Consultation Document from Amarin Pharma**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. HEART UK – The Cholesterol Charity

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using icosapent ethyl in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: January 2022

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using icosapent ethyl in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: Tuesday 22 February 2022

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 3.

1 Recommendations

1.1 Icosapent ethyl is not recommended, within its marketing authorisation, for reducing the risk of cardiovascular events in adults who:

- have a high cardiovascular risk with raised triglycerides (150 mg/dL [1.7 mmol/litre] or more) and
- are having statins and
- have established cardiovascular disease, or
- diabetes and at least 1 other cardiovascular risk factor.

1.2 This recommendation is not intended to affect treatment with icosapent ethyl that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

There are currently no treatment options to reduce the risk of cardiovascular events in people taking statins who have raised triglycerides.

Clinical trial evidence suggests that icosapent ethyl reduces the risk of cardiovascular events in people who have established cardiovascular disease (secondary prevention). The evidence on its use by people without established cardiovascular disease but who have diabetes and at least 1 cardiovascular risk factor (primary prevention) is less clear. It is also uncertain how well icosapent ethyl works because it was compared with a placebo that may itself increase cardiovascular risk. Also, the trial may not be generalisable to the NHS.

The cost-effectiveness estimates for icosapent ethyl are uncertain. This is because there are several concerns with the company's economic model, including its structure, how treatment effect was modelled and what happens when people stop having treatment.

Further information and analyses are needed to address the uncertainties. So, icosapent ethyl is not recommended.

2 Information about icosapent ethyl

Marketing authorisation indication

2.1 Icosapent ethyl (Vazkepa, Amarin Corporation) is indicated 'to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL [1.7mmol/l]) and established cardiovascular disease or diabetes, and at least one other cardiovascular risk factor'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 Icosapent ethyl costs £173 per pack of 120 capsules (including VAT; company submission). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee considered evidence submitted by Amarin Corporation, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway and comparator

People with elevated triglycerides who are having statins with or without ezetimibe would welcome a treatment option

3.1 NHS England estimate that between 25% and 35% of people having statin therapy have elevated triglycerides. The patient and clinical experts explained there is an unmet need for this population. This is because

there are no pharmaceutical treatments for people at risk of cardiovascular events who have elevated triglycerides despite having statins with or without ezetimibe. They explained the aim of treatment would be to reduce the risk of cardiovascular events. The patient expert commented that lifestyle changes, including diet and exercise can be helpful at reducing risk of cardiovascular events. The patient expert noted the importance of treatment options because current ways of reducing cardiovascular risk may not work for everyone. The committee concluded that people with elevated triglycerides who are having statins with or without ezetimibe would welcome a treatment option.

Statins with or without ezetimibe is an appropriate comparator

3.2 The marketing authorisation for icosapent ethyl says it should be used in addition to statin therapy. The company submission, which was based on the REDUCE-IT trial (see section 3.6), also noted people could have ezetimibe in addition to statins. The clinical experts said that fibrates are not used to reduce the risk of cardiovascular events in people with moderately elevated triglycerides. They explained that fibrates are used by people with very high triglycerides to prevent pancreatitis, which is a different indication. The clinical experts confirmed that there are no treatments to reduce cardiovascular risk for people with elevated triglycerides who have statins with or without ezetimibe. Therefore, the committee agreed statins with or without ezetimibe was the appropriate comparator.

Icosapent ethyl is likely to be used mostly in a primary care setting

3.3 The company noted it expected icosapent ethyl to be used in a primary care setting. The clinical experts commented that icosapent ethyl would be used in both primary and secondary care settings but it would likely be used more in primary care. The committee concluded icosapent ethyl would likely be used mostly in a primary care setting.

Population

The population in the company's submission is narrower than the marketing authorisation in terms of LDL-C levels and is acceptable

3.4 Icosapent ethyl's marketing authorisation does not specify age or LDL-C thresholds (see section 2.1). However, the company only provided evidence for icosapent ethyl from the REDUCE-IT trial. This included people aged 45 and over who had cardiovascular disease, and people aged 50 and over who had diabetes and at least 1 other cardiovascular risk factor (see section 3.5). The trial also only included people with LDL-C levels above 1.04 mmol/litre and less than or equal to 2.60 mmol/litre. A clinical expert noted that there are people younger than 45 who have cardiovascular disease and elevated triglycerides in the NHS. They explained that many of these people have South Asian family backgrounds. The ERG commented that the treatment effect for icosapent ethyl varies by age, with a larger benefit observed in people under 65 (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.56 to 0.75) than in people aged 65 or older (HR 0.87, 95%CI 0.76 to 1.00). The committee was aware that restricting by age may result in an equalities issue and would consider this in its decision making (see section 3.18). The committee concluded the company's submission for icosapent ethyl was narrower than the marketing authorisation and it was acceptable to use the LDL-C thresholds from REDUCE-IT.

It is appropriate to consider the effects of icosapent ethyl separately for the primary and secondary prevention subgroups

3.5 The company provided evidence for 2 separate risk groups from the REDUCE-IT trial: primary and secondary prevention. The primary prevention group included people aged 50 and over with type 1 or 2 diabetes and at least 1 additional cardiovascular risk factor. The risk factors included being aged 55 or over, cigarette smoking, hypertension, high-density lipoprotein cholesterol levels below 1.04 mmol/litre, high-

sensitivity C-reactive protein above 3.0 mg/litre, renal dysfunction, retinopathy, micro- or macroalbuminuria, or ankle-brachial index below 0.9. People in the secondary prevention group were aged 45 years and over with established cardiovascular disease. The committee noted these subgroups were clinically distinct and concluded it was appropriate to consider the effects of icosapent ethyl separately for primary and secondary prevention.

Clinical evidence

The generalisability of the results from REDUCE-IT to the NHS in England is uncertain

3.6 The company provided clinical evidence from REDUCE-IT, a randomised trial comparing icosapent ethyl with a mineral oil placebo. The trial included people in primary and secondary prevention groups (see section 3.5). The trial included people who had statins with or without ezetimibe, triglyceride levels of above 1.53 mmol/litre and below 5.64 mmol/litre, and LDL-C levels of 1.04 mmol/litre to 2.60 mmol/litre. In the trial, 8,179 people were randomised and 29% were in the primary prevention group and 71% were in the secondary prevention group. The primary endpoint was time from randomisation to the first occurrence of any component of the major adverse cardiovascular event (MACE) composite outcome, which included: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation or unstable angina. The ERG noted that REDUCE-IT did not include any people from the UK, which increases uncertainty around the generalisability of the results to the NHS in England. A clinical expert commented that the trial did not represent the ethnic diversity in England. They noted that people with South Asian family backgrounds may benefit more from icosapent ethyl. The company compared the baseline characteristics of the primary and secondary prevention subgroups with similar populations from Steen et al. 2016. This was a retrospective study of 183,565 people with or without atherosclerotic cardiovascular disease

from The Health Improvement Network database in the UK. The company noted that age, gender, BMI and systolic blood pressure were similar between REDUCE-IT and Steen et al. The exact values from REDUCE-IT are considered confidential by the company and cannot be reported here. However, the ERG noted that there were substantial differences between REDUCE-IT and Steen et al. that might modify treatment effect. It also questioned the relevance of Steen et al. because the study is 5 years old. The clinical adviser to NHS England raised additional concerns about REDUCE-IT's generalisability based on the current management of high-risk cardiovascular disease and diabetes. They noted that several treatments available in the NHS were used by only a small proportion of people in REDUCE-IT or not at all. The adviser noted inclisiran, which is recommended by NICE for treating primary hypercholesterolaemia or mixed dyslipidaemia as an adjunct to diet in adults, was not a permitted concomitant treatment in REDUCE-IT. Therefore, the effect of icosapent ethyl on reducing the risk of cardiovascular disease in people who have inclisiran is unknown. The clinical adviser also commented that standard care in the NHS for diabetes includes SGLT2 inhibitors but it is uncertain how many people in REDUCE-IT had these treatments. They explained that the treatment landscape for high-risk cardiovascular disease and type 2 diabetes in the NHS in England makes the generalisability of REDUCE-IT uncertain. The committee concluded that the generalisability of the results from REDUCE-IT to the NHS in England was uncertain.

Icosapent ethyl's mechanism of action is not fully understood, which adds uncertainty

3.7 The company stated that icosapent ethyl's mechanism of action is not fully understood. The company noted it appears to modulate the atherosclerosis pathway by lipid and non-lipid effects. It explained the primary lipid effect is reducing triglyceride levels. It added that the non-lipid effects may include localised anti-inflammatory effects, regulation of lipid metabolism gene transcription, antithrombotic effects and plaque reduction. The clinical experts also commented that the mechanism of

action is uncertain. They explained that the reduction in cardiovascular risk observed in REDUCE-IT was larger than what would be expected from a reduction in triglycerides alone. The committee concluded that the mechanism of action is not fully understood, which adds uncertainty to the trial's results.

The treatment effect of icosapent ethyl is uncertain because of the mineral oil placebo in REDUCE-IT

3.8 The placebo group in REDUCE-IT had 4 g of light mineral oil per day. In the intention to treat population, icosapent ethyl significantly reduced the risk of a composite MACE outcome compared with placebo (HR 0.75, 95% CI 0.68 to 0.83). Icosapent ethyl significantly reduced the first occurrence of the MACE outcome in the secondary prevention subgroup compared with placebo (HR 0.73, 95% CI, 0.65 to 0.81). A similar trend was reported for the primary prevention subgroup, although it was not statistically significant (HR 0.88, 95% CI, 0.70 to 1.10). A professional group and the NHS England clinical adviser expressed concerns about the REDUCE-IT results, in part because of the use of mineral oil. They commented that mineral oil was not a true neutral oil and may have increased the risk of a cardiovascular event in the placebo group. This would exaggerate the observed difference in cardiovascular events between the icosapent ethyl and placebo groups. The professional group and NHS England clinical adviser also commented that results of a similar trial, STRENGTH, did not show the same magnitude of benefit as REDUCE-IT. STRENGTH compared a combination of eicosapentaenoic acid and docosahexaenoic acid, which is similar to icosapent ethyl, with a corn oil placebo. The NHS England clinical adviser explained they expected to see analyses where the magnitude of treatment effect was reduced by 7% to account for the estimated negative effect of mineral oil. The committee noted that this should be done by re-estimating the relative effects by adjusting the placebo group. The ERG explained that the Takahito et al. 2021 paper comparing REDUCE-IT with STRENGTH suggested the differences in results might be partially explained by

differences in placebo comparators. But it cautioned that there were other possible explanations, including that corn oil could decrease the risk of MACE or that there were underlying differences in patient characteristics between the trials. The ERG highlighted a systematic review by Olshansky et al. 2020 that concluded mineral oil at the quantities used as placebos likely does not significantly affect study conclusions. However, the ERG noted the systematic review had some limitations and one of the co-authors was employed by Amarin. The committee noted that the effect of icosapent ethyl is uncertain because of the mineral oil placebo. The committee was aware that the European Medicines Agency reported analyses by the company suggesting the putative negative effect of mineral oil should not account for more than 3% of MACE events. The committee also noted the Takahito et al. paper commented there was an unexplained additional 13% benefit in REDUCE-IT. It concluded it would like to see scenarios where the magnitude of the treatment effect was reduced by 7% and 13%.

Icosapent ethyl has manageable adverse events

3.9 In REDUCE-IT, similar proportions of people having icosapent ethyl (81.8%) and placebo (81.3%) reported adverse events. The most commonly reported adverse events among people having icosapent ethyl were diarrhoea (9.0%), back pain (8.2%) and hypertension (7.8%). The company noted that diarrhoea occurred statistically more frequently among people who had placebo (11.1%) than icosapent ethyl (9.0%). The clinical experts noted icosapent ethyl appears to be generally well tolerated. But they had some concerns around specific adverse events. In REDUCE-IT, there were significant differences in the incidence of atrial fibrillation (5.3% icosapent ethyl, 3.9% placebo), bleeding-related events (11.8% icosapent ethyl, 9.9% placebo), constipation (5.4% icosapent ethyl, 3.6% placebo) and peripheral oedema (6.5% icosapent ethyl, 5.0% placebo). The committee noted that some fish oil products can be associated with unpleasant burps that may affect adherence. The

company explained that reports of burps related to icosapent ethyl were relatively low, although it did not have an exact figure. The committee would have preferred to see the proportions of people experiencing burps in each treatment group. The committee noted the concerns about some adverse events, but concluded icosapent ethyl was generally well tolerated with manageable adverse events.

The economic model

The results from the company's model are uncertain and more information is needed

3.10 The company's model included 8 health states: cardiovascular event free, first event, post-first event, second event, post-second event, third or more event, post-third or more event, and death. The events in the model were based on the composite 5-point MACE outcome from REDUCE-IT (see section 3.6). The health states were populated by fitting parametric models to the Kaplan–Meier curves for first, second and third plus cardiovascular events from REDUCE-IT following a partitioned survival approach. The model used a 1-day cycle length and a lifetime horizon, equivalent to 36 years. The company used baseline utility values from the literature (Stevanovic et al. 2016 and O'Reilly et al. 2011) and health state multipliers from NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification. The ERG noted several concerns with the model structure and differences from models for similar appraisals, including that it used a partitioned survival type approach to estimate the probability of having a cardiovascular event. The ERG was concerned that the model structure assumed independence of endpoints, meaning the probability of having a second or third cardiovascular event was independent of the time of the previous events. It commented the company's model did not explicitly model nonfatal cardiovascular events, it used a 1-day cycle length, and there was uncertainty in the time to event analysis (see section 3.12). The

committee noted that it had not seen evidence that the company's model could predict the survival from REDUCE-IT. The committee commented that it was unusual that the company's entire model was based on REDUCE-IT, rather than applying the relative treatment effect observed in the trial to a baseline risk estimated using routine datasets. The committee concluded that the results of the company's model were uncertain because of the model structure and more information was needed before it can be used for decision making.

Using the composite 5-point MACE outcome in the model increases uncertainty

3.11 The company's model used the same composite MACE outcome as REDUCE-IT (see section 3.6). The ERG was concerned that the composite outcome could mask the treatment effect in relation to individual cardiovascular events. The ERG highlighted that the hazard ratios for cardiovascular death in the intention to treat population (HR 0.80, 95% CI 0.66 to 0.98) and death from any cause (HR 0.87, 95% CI 0.0.74 to 1.02) were larger than that for the composite 5-point MACE (HR 0.75, 95% CI 0.68 to 0.83). The ERG noted it would like to see smoothed empirical hazard plots for each individual event included in the MACE outcome. The company noted that although the composite outcome was used, the distribution of specific cardiovascular events was applied in the model. The company explained that the effect of icosapent ethyl on each specific event occurring as a first, second or third plus event was taken into account. However, the ERG commented that applying direct estimates of time to each event is not necessarily equivalent to the combination of time to the composite and proportion of the composite attributed to each event. The clinical experts commented that the composite MACE outcome is common for large clinical trials but one expert said that there was some debate about if all components of the MACE should be used. The committee was concerned that the composite outcome might be double counting risk. It noted that revascularisations

accounted for a large proportion of second and third events (the exact values are considered confidential by the company and cannot be reported here). It noted that coronary revascularisation could be an indicated procedure based on a preceding event, such as myocardial infarction. The committee concluded the composite 5-point MACE outcome increases uncertainty and it would like to see the Kaplan–Meier curves and hazard ratios for each of the individual cardiovascular events.

Additional information and analyses are needed for the company's updated time to event modelling

3.12 The company originally fitted separate parametric models to the icosapent ethyl and placebo arms for first, second and third plus events in REDUCE-IT. The ERG noted the company had not followed the Decision Support Unit's technical support document 14. Specifically, the company used independent survival models without considering proportional hazards. The ERG also highlighted that the company had not provided the full time to event analysis, including fitted models and justification for selection, at technical engagement. In response, the company updated its time to event analysis. It tested the proportional hazards assumption and fitted 1 parametric model to the full Kaplan–Meier curve for each composite event, with treatment group as a covariate, following technical support document 14. The company also provided the updated models and the statistical fit for each. Because the company's updated time to event analysis was submitted after technical engagement, the ERG did not have enough time to fully validate it before the committee meeting. The ERG did highlight that the model allowed different curves to be selected for each treatment group, suggesting that it was not a jointly modelled approach. The committee agreed that the company should explain this and why the Weibull curve could not be fitted. It noted that it could be reasonable to fit independent models to each treatment group without using a hazard ratio even if the proportional hazards assumption was met. The ERG noted that the time to event analysis was only

provided for the intention to treat population and not for the primary and secondary prevention subgroups. It also noted that different parametric curves might be more suitable for the subgroup analyses. The committee noted that the company should also provide internal and external validation of the subgroup extrapolated curves. This should include a comparison of model-predicted overall survival compared with overall survival in REDUCE-IT. This should also consider clinical expert judgements on the plausibility of the long-term model predictions of having 0, 1, 2 or 3 plus events, and overall survival. The committee concluded the company need to provide additional information and analyses for its updated time to event modelling to allow this to be fully critiqued before it could be considered suitable for decision making.

The modelling of treatment waning and time to treatment discontinuation are not appropriate

3.13 The company's base case assumed that the treatment effect for icosapent ethyl continued at the same level for the duration of the model with no treatment waning. The company commented that similar recent appraisals did not include treatment waning, including the appraisals of inclisiran (TA733), evolocumab (TA394) and alirocumab (TA393). The company provided an analysis of treatment effect over time, which showed the treatment effect did not decrease during the follow up period (the exact values are considered confidential by the company and cannot be reported here). The ERG noted that the confidence interval for the primary prevention subgroup crossed 1 in the follow-up period. The ERG also noted that the clinical trial was shorter than the modelled time horizon, so there is unresolvable uncertainty about the long-term treatment benefits. The ERG's preferred assumption was to include a 10-year post-trial treatment waning effect for all events. The clinical expert commented that given the absence of long-term data it is difficult to determine the appropriateness of a treatment waning assumption. However, the expert noted that related treatments for cardiovascular disease, such as statins,

have long-term effects. The expert commented that the company's assumption of no treatment waning was likely reasonable. The committee noted that in the recent related appraisal of bempedoic acid and ezetimibe (TA694), the company's model assumed results achieved at 12 weeks were maintained for the duration of the model's time horizon, or until treatment was stopped. It was concerned that treatment discontinuation was not linked to treatment effect in the icosapent ethyl model. It would have liked to see the full analysis for time to treatment discontinuation, including for subgroups. The committee concluded it would have preferred a method linking treatment effect and discontinuation by changing the hazard ratio to 1 at an appropriate time after people stopped icosapent ethyl.

Non-cardiovascular-related deaths hazard ratios are uncertain

3.14 The company's model included mortality for cardiovascular-related death and non-cardiovascular-related death. The model used non-cardiovascular-related death hazard ratios for icosapent ethyl and the placebo groups separately. The ERG commented that it was not clear why non-cardiovascular death should be treatment dependent because cardiovascular death is already captured in the model. It preferred to apply a weighted average of the hazard ratios for non-cardiovascular-related death by health state to both treatment groups. The company disagreed with the ERG's method because the averages were calculated for the intention to treat population and did not account for the proportion of people in the primary versus secondary prevention subgroups. The company elaborated that people in the two subgroups are not comparable. It added that diabetes and number of prior events were non-cardiovascular-related death modifiers. The committee concluded the non-cardiovascular-related death hazard ratios are uncertain and it would like to see evidence that diabetes and number of previous events are non-cardiovascular-related death modifiers.

The company's model has uncertainties that should be addressed before it is compared with the validation model

3.15 Due to the ERG's concerns with the company's model, the company provided a microsimulation model for validation. The validation model was originally developed for the US setting but was adapted to a UK NHS setting by using the same costs, utilities and background mortality as the company's model. The validation model also used cardiovascular event data from REDUCE-IT. The company provided a comparison of its model with the validation model. The validation model explicitly modelled individual nonfatal cardiovascular events, had a cycle length of 6 months and assumed people experienced an acute utility for 18 months following an event, after which they experienced a post-event utility. The company also provided a 30-year comparison of the expected number of first, second and third events, people discontinuing icosapent ethyl, and people alive in the company's and validation models. It noted the models produced similar clinical estimates. The ERG noted that additional details on the discrepancies in the original cross validation and explanation for the remaining differences in the updated cross validation would be helpful. The committee concluded that there were unresolved uncertainties in the company's model that should be addressed before comparison with the validation model.

Cost-effectiveness estimates

Because of the uncertainty an acceptable ICER is around £20,000 per QALY gained

3.16 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee

will be more cautious about recommending a technology if it is less certain about the ICERs presented.

The committee noted the high level of uncertainty, specifically:

- the generalisability of the clinical trial results to the NHS in England (see section 3.6)
- the robustness of the clinical-effectiveness results because of the mineral oil placebo (see section 3.8)
- the differences in results from the REDUCE-IT and STRENGTH trials (see section 3.8)
- the appropriateness of the company's model (see section 3.10)
- the composite 5-point MACE outcome in the model (see section 3.11)
- how treatment waning and time to treatment discontinuation were modelled (see section 3.13).

Therefore, it agreed that an acceptable ICER would be around £20,000 per QALY gained. The committee noted that additional analyses and information were needed for decision making. The committee would have preferred:

- scenarios in which the treatment benefit of icosapent ethyl from REDUCE-IT is reduced by 7% and 13% (see section 3.8)
- the Kaplan–Meier curves, hazard ratios and empirical hazard plots for each individual event from the composite MACE outcome (see section 3.11)
- a comparison of model-predicted overall survival compared with overall survival in REDUCE-IT (see section 3.12)
- full time to event analysis, following technical support document 14, for the primary and secondary prevention subgroups, including clarity on the updated time to event analyses, consideration of clinical expert judgements on the plausibility of the long-term model predictions of having 0, 1, 2 or 3 plus events and overall survival (see section 3.12)

- full analysis for time to treatment discontinuation, including for subgroups (see section 3.13)
- treatment effect and discontinuation linked so that when people stop icosapent ethyl, the hazard ratio changes to 1 at an appropriate time, including scenarios for all 6 potential models for time to treatment discontinuation (see section 3.13)
- further evidence that diabetes and number of prior events are non-cardiovascular-related death modifiers (see section 3.14)
- detail on the discrepancies in the original cross validation and explanation for the remaining discrepancies in the updated cross validation (see section 3.15).

Icosapent ethyl is not cost effective for reducing the risk of cardiovascular events

3.17 The company's base case included the updated time to event analysis, assumed no treatment waning for icosapent ethyl, and used the exponential curve to extrapolate time to treatment discontinuation. The company's base case results for icosapent ethyl compared with a stable dose of statins with or without ezetimibe were:

- £28,266 per QALY gained for the intention to treat population
- £22,796 per QALY gained for the secondary prevention subgroup
- £85,438 per QALY gained for the primary prevention subgroup.

Because the company's base case was based on time to event analysis submitted after technical engagement, the ERG did not have sufficient time to update its base case. In its previous base case, the ERG's cost-effectiveness estimates were much higher than the company's and above the threshold NICE normally considers a cost-effective use of NHS resources. The committee noted the uncertainty with the economic model and the additional information that was needed to inform decision making. It noted that due to the additional analyses and information needed from the company that it did not have a committee-preferred ICER. However,

the committee noted that the company's own ICER for the primary prevention subgroup was much higher than what NICE normally considers an acceptable use of NHS resources. It therefore concluded that the primary prevention subgroup was very unlikely to be cost effective in any additional analyses. It also recalled that it was appropriate to consider each clinically distinct subgroup separately (see section 3.5). Therefore, it would be appropriate for the company to only provide additional analyses and information for the secondary prevention subgroup. The committee concluded that given the uncertainty and the company's base case ICERs, icosapent ethyl could not be recommended for any of the populations considered.

Other factors

The committee considered potential equality issues in its decision making

3.18 A patient organisation and clinical expert raised several potential equalities issues. They noted that people with Black, Asian and minority ethnic family backgrounds are more likely to have elevated triglycerides. The patient organisation also commented that people living in England's most deprived areas are almost 4 times more likely to die prematurely from cardiovascular disease than those in the least deprived. It also explained that compared with the general population, people with severe mental illness are more likely to develop and die from preventable conditions, including cardiovascular disease. It also noted that people with learning disabilities are at increased risk of developing cardiovascular disease. The clinical expert noted that some religions have restrictions on fish products. The committee considered these to be important issues. The committee concluded that its recommendation for icosapent ethyl would apply to all patients and that the recommendation would not affect people protected by the equality legislation any differently.

End of life criteria do not apply

3.19 NICE's advice about life-extending treatments for people with a short life expectancy did not apply.

The committee has not seen evidence of additional benefits that are not captured in the cost-effectiveness analysis

3.20 The clinical experts noted that icosapent ethyl may be considered innovative because it appears to work on a disease pathway that is not fully understood. The committee concluded that it had not seen evidence of additional gains in health-related quality of life associated with icosapent ethyl over those already included in the QALY calculations.

Conclusion

Icosapent ethyl is not recommended for reducing the risk of cardiovascular events in people with elevated triglycerides

3.21 The committee noted uncertainty in the clinical effectiveness evidence for icosapent ethyl because of the mineral oil placebo (see section 3.8). It also noted concerns about the generalisability of the trial results to the NHS in England (see section 3.6). It was concerned about the company's modelling approach (see section 3.10), including how the treatment effect after discontinuation was modelled (see section 3.13) and the composite outcome (see section 3.11). The committee noted that the company's updated time to event analysis had not been fully validated by the ERG and requested additional information and analyses. It noted the company's base case results were all above £20,000 per QALY gained. Therefore, the committee concluded that icosapent ethyl is not recommended for reducing the risk of cardiovascular events in people with elevated triglycerides.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
January 2022

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Catie Parker

Technical lead

Alex Filby

Technical adviser

Louise Jafferally

Project manager

ISBN: [to be added at publication]

NICE National Institute for Health and Care Excellence

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Tuesday 22 February 2022**. Please submit via NICE Docs.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Amarin**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]
Comment number	**Comments**
1	**General comment / cover letter** Dear Appraisal Committee Members, Amarin welcomes the opportunity to comment on this Appraisal Consultation Document (ACD), and kindly ask the Committee to reconsider the recommendation published in the ACD. Amarin would like to outline the full extent of the unmet need. In the UK, it is estimated that there are 7.6 million people living with cardiovascular disease (CVD), which could increase in the coming years due to an ageing and growing population. It is a common cause of death, accounting for more than a quarter (27%) of all deaths in the UK and is the largest cause of premature mortality.[1] The ongoing coronavirus pandemic (COVID-19) has also resulted in many patients being undertreated, further highlighting the urgent need for a treatment that can prevent cardiovascular (CV) events. The REDUCE-IT trial has demonstrated that icosapent ethyl significantly reduces CV events in high-risk adult statin-treated patients with hypertriglyceridemia. Benefits were consistently observed across individual and composite endpoints, with icosapent ethyl coming across as safe and well tolerated by the study participants.[2] No treatments are currently recommended in the UK specifically for the prevention of CV events in patients with established CVD or diabetes, with hypertriglyceridemia, who have controlled LDL-C levels and are on a stable dose of statins. Hence, there is high unmet need for the introduction of a drug such as icosapent ethyl, which is the only therapy recommended in the European Society of Cardiology (ESC) guidelines, in combination with a statin, for the treatment of patients with hypertriglyceridemia.[3]

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	As part of this response, Amarin have addressed the concerns raised by the Committee and Evidence Review Group (ERG) in the appraisal consultation document, specifically: • The generalisability of the REDUCE-IT trial results to UK clinical practice was demonstrated by undertaking a comparison between the REDUCE-IT trial population and a real-world high-risk cohort from a UK retrospective study, showing similar baseline characteristics between both cohorts.[4] Furthermore, CV risk in the REDUCE-IT trial was identified as being similar to that observed in two recent observational studies in Western populations which are demographically similar to the UK population.[5,6] • The issue of the neutrality of the mineral oil placebo used in the REDUCE-IT trial was thoroughly examined by the European Medicines Agency (EMA) and the US Food and Drugs Administration (FDA).[7,8] Both authorities concluded that a putative negative effect of mineral oil should not account for more than 0.3 – 3% of 5-point MACE events and that even when assuming the unlikely worst-case scenario, the remaining beneficial effect of icosapent ethyl on MACE events can be considered robust and meaningful. The range 7-13% reduction in treatment effect suggested by the Committee was derived from a single observational study in a Danish population that simulated the effect of varying lipid and CRP parameters in a population attempting to mimic REDUCE-IT; this study was criticised by the ERG. Therefore, Amarin see no plausibility to model a reduction in treatment effect for icosapent ethyl. • The clinical outcomes estimated by the economic model were further validated by three UK clinical experts engaged during the ACD consultation period. All three experts agreed with the long-term estimates produced and, highlighted that these align with what they would expect to observe in real-world UK clinical practice. A cross-validation was also undertaken with the external Markov model which has just been published, to compare the outputs between both models.[9] The long-term clinical estimates produced from both models were similar, leading to very close incremental cost-effectiveness ratios (ICERs) and, demonstrating that the partitioned survival approach adopted robustly predicts outcomes in line with more conventional models in this area. • Regarding treatment waning, there is no clinical evidence to suggest that the treatment effect of icosapent ethyl will reduce over time. This is further supported by the Kaplan-Meier curves for the 5-point MACE composite endpoint from REDUCE-IT, which demonstrate that the treatment effect of icosapent ethyl increases over time before stabilising. Furthermore, no treatment waning was applied in previous appraisals within a similar disease area.[10–12]

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	• There is substantial evidence in the literature confirming that a diagnosis of diabetes is associated with non-CV related death, and that reducing total nonfatal CV events has a statistically significant effect on non-CV related deaths.[13,14] This has also been confirmed by the three UK clinical experts consulted. Therefore, it is appropriate to consider non-CV related mortality hazard ratios in the economic model. Taking into account the suggestions and recommendations from the Committee and the ERG, Amarin have provided a revised company base case. Changes include focussing on the secondary prevention population only, inclusion of treatment independent non-CV related mortality hazard ratios, applying a Weibull distribution to inform the time-to-treatment discontinuation curve (based on best statistical fit), adjusting background mortality to solely include non-CV related mortality, and a revision of the list price of icosapent ethyl from £173.00 per pack of 120 capsules, to £[redacted]. Applying the above changes in the economic model results in a revised base case ICER of £19,848 for the secondary prevention population. A detailed summary of the key uncertainties raised by the Committee and how each of these has been addressed can be found in Sections 1 – 14. All new evidence has been provided in the appendix at the end of this document.
2	**Icosapent ethyl is likely to be used mostly in a primary care setting** Amarin agree with the Committee conclusion that icosapent ethyl will most likely be used in a primary care setting.
3	**Generalisability of the REDUCE-IT trial results to the NHS in England** In section 3.6 of the ACD, it was noted that: "*The committee concluded that the generalisability of the results from REDUCE-IT to the NHS in England was uncertain*". Amarin would like to refer the Committee to the response to Key Issue 4 given during the initial technical engagement, in which a comparison was made between the REDUCE-IT clinical trial population and a retrospective examination of lipid-lowering treatment patterns in a real-world high-risk cohort in the UK in 2014, conducted using The Health Improvement Network (THIN) database by Steen *et al.*[4] For completeness, the comparison between the established ASCVD (secondary prevention) group from REDUCE-IT and the equivalent population from Steen *et al.* is replicated in Table 1.

	In the secondary prevention population, BMI and systolic BP were similar between studies, though the mean age was higher in Steen *et al.* and the percentage of male patients was higher in REDUCE-IT. In the REDUCE-IT trial, a larger proportion of patients had recent ACS, other CHD, diabetes, hypertension, or a history of CHF. However, ischaemic stroke/TIA and PAD were slightly more common in Steen *et al*. CKD incidence was similar in both studies.[4] The proportion of patients treated with a low or high intensity statin was very similar between studies, though a larger proportion of patients were treated with a medium intensity statin, anti-platelet, ACE inhibitor, ARB, or beta-blocker in the REDUCE-IT trial. In regard to the generalisability of CV risk between REDUCE-IT and the UK population, two recent observational studies in Western populations demographically similar to the UK population have demonstrated similar levels of residual CV risk. Lawler *et al.* examined the incidence of moderately elevated triglycerides and associated CV outcomes in 196,000 Canadian patients with established ASCVD.[5] In this population, among those older than 66 years with available prescription drug information, 80% of individuals were prescribed statins and rates of non-statin lipid-lowering therapies were: ezetimibe (11.7%), fenofibrate (2.4%), gemfibrozil (0.1%), bezafibrate (0.1%), and niacin (0.6%). Over a median follow-up of 3 years, first occurrence of the composite outcome myocardial infarction (MI), unstable angina, stroke or transient ischemic attacks, coronary revascularization, or CV death occurred at a rate of between 42.19 – 57.56 per 1,000 person-years, for patients with triglycerides in the range 1.5 - >4mmol/L.[5] This compares with a rate of [redacted] in the established ASCVD population in the REDUCE-IT trial, over a median of 4.9 years. Similarly, Ferrières *et al.* investigated a French cohort of post-MI patients enrolled based on similar eligibility criteria to the REDUCE-IT trial, with 97.7% of patients on moderate- or high-intensity statin therapy and 8.7% on ezetimibe. The rate of the composite outcome of all-cause death, nonfatal MI, or nonfatal stroke was 36.7 per 1,000 patient years.[6] This is again comparable to the rate of 36.9 per 1,000 for the key secondary endpoint, the composite of CV death, non-fatal MI and non-fatal stroke, in the cohort of patients with established ASCVD in the REDUCE-IT trial.[7] With respect to the clinical expert comment that the REDUCE-IT trial did not represent the ethnic diversity in England, Amarin note that the most recent census conducted in England & Wales by the Office for National Statistics indicated 84.8% of the population identified their ethnicity as Caucasian.[15] This compares to 90.3% identifying as 'white-race' in the REDUCE-IT trial. Furthermore, no interaction was observed for the benefit of icosapent ethyl in reducing the risk of CV events according to race in the REDUCE-IT trial (5-point MACE primary endpoint: white HR 0.77, 95% CI 0.69-0.85; non-white

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	HR 0.60, 95% CI 0.43-0.83). Amarin also note that the people from South Asian ethnic background have higher incidence of coronary heart disease and diabetes compared to other ethnicities, and people of Black African, West African and Caribbean origin have high incidence of stroke.[16] Therefore, ethnic minority populations would likely benefit from access to a broader range of CV risk reducing therapies. In regard to the clinical adviser's comments on the availability of other risk reducing medications to the NHS, there was limited but relevant use of several anti-diabetic agents known to reduce CV risk in the REDUCE-IT trial, namely SGLT2 inhibitors ([redacted]) and GLP-1 agonists ([redacted]). Rates of use of these agents were consistent with the time-period in which the trial was conducted and the evidence for CV risk reduction available at the time (2011-2018, e.g. the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial was published in 2015, the Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes was published in 2016). Use of PCSK9 inhibitors was an exclusion criterion for the REDUCE-IT trial. However, contemporary uptake of these agents remains very low. A recent observational study conducted in 18 European countries, including >500 patients from the UK, demonstrated use of PCSK9 inhibitors in only 1.1% of patients with established ASCVD.[17] Furthermore, NICE reimbursement of currently available agents in England & Wales is restricted to high and very high-risk patients with LDL-C persistently above 3.5mmol/L, in case of alirocumab and evolocumab, and above 2.6mmol/L in the case of inclisiran.[10–12] Besides, the mechanism by which icosapent ethyl lowers CV risk is independent of LDL-C (Figure 2). Therefore, Amarin do not believe PCSK9 inhibitors are a relevant treatment consideration for icosapent ethyl.
4	**Icosapent ethyl's mechanism of action** As stated in the Summary of Product Characteristics (SmPC), icosapent ethyl is a stable ethyl ester of the omega-3 fatty acid, eicosapentaenoic acid (EPA). The mechanisms of action contributing to reduction of CV events with icosapent ethyl are not completely understood. The mechanisms are likely multi- factorial including improved lipoprotein profile with reduction of triglyceride-rich lipoproteins, anti-inflammatory, and antioxidant effects, reduction of macrophage accumulation, improved endothelial function, increased fibrous cap thickness/stability, and antiplatelet effects. Each of these mechanisms can beneficially alter the development, progression, and stabilisation of atherosclerotic plaque, as well as the implications of plaque rupture, and preclinical and clinical studies support such benefits with EPA[18]. It is noteworthy that other treatments recently reviewed by NICE, such as SGLT2 inhibitors have an uncertain mechanism of action in relation to benefits such as reducing heart failure (HF) and delaying CKD progression.[19,20]
5	**Mineral oil placebo in REDUCE-IT**

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	With regard to the concerns about the neutrality of the mineral oil placebo raised by the NHS England clinical adviser which may have marginally altered the observed difference in CV events between the icosapent ethyl and placebo groups, Amarin would like to draw the committee's attention to the following points: Large doses (15-45 ml) of food grade mineral oil have been used safely for decades to treat constipation in children. Pharmaceutical-grade mineral oil has a purity and chemical structure that differs substantially from food-grade or technical-/industrial-grade mineral oils. Pharmaceutical grade mineral oil is manufactured under Good Manufacturing Practices at facilities subject to inspections by regulatory bodies and is identified by the European Union as a substance/active ingredient that does not pose a risk.[21] Following discussion with the US Food and Drugs Administration (FDA), pharmaceutical grade mineral oil (2 x 1 g capsules, containing approximately 1 mL fill volume of mineral oil per placebo capsule to match the active capsule fill volume, twice daily) was selected as the placebo for the REDUCE-IT trial because its colour and consistency closely matched that of the investigational medicinal product, icosapent ethyl. Furthermore, other potentially suitable oils including olive, corn, safflower, sunflower, and coconut oils were discounted as they contain saturated, monounsaturated, and omega-6 polyunsaturated fatty acids.[22] The ERG also made this observation as part of the technical engagement: *"A plausible explanation for the difference between mineral oil and corn oil is that corn oil decreases the risk of MACE and that the changes observed in the REDUCE-IT placebo arm are part of the natural history*." The question of whether mineral oil could have had a negative effect on the placebo event rate in REDUCE-IT has arisen largely because of small numerical increases in several laboratory parameters that are known to correlate with CV risk in the placebo arm of the trial. These changes are summarised in Table 2.[2] The degree that these changes represented the natural course of the disease, was due to variability and regression of the mean effects, or represented a negative effect of mineral oil is not entirely clear. An analysis of LDL-C percentage changes in CV outcome trials with statin-treated cohorts from 2003 to 2019 showed that 79% of studies reported increases in LDL-C after statin stabilization similar to those observed in the placebo arm of the REDUCE-IT trial (Figure 1).[22] Post-hoc analyses of the REDUCE-IT trial also do not demonstrate any association between the level of LDL-C and the event rate in the placebo arm of the trial or the benefit of icosapent ethyl vs. placebo (Figure 2 and Figure 3). A recent systematic literature review including 80 studies that used some form of mineral oil as a placebo by Olshansky *et al.*, which was also

	highlighted by the ERG, concluded that it '*does not meaningfully affect study conclusions when used as a placebo at the quantities used in clinical trials'*.[22] The issue of the neutrality of the mineral oil placebo was examined in detail by both the EMA / Medicines and Healthcare products Regulatory Agency and the FDA. In both cases, the authorities concluded that "…*a putative negative effect of mineral oil should not account for more than 0.3 – 3% of 5-point MACE events. In summary, it is concluded that even when assuming the unlikely worst-case scenario, the remaining beneficial effect of Vazkepa on MACE events can be considered robust and meaningful."* [7,8] The range 7-13% reduction in treatment effect suggested by the Committee is derived from a single observational study in a Danish population that simulated the effect of varying lipid and CRP parameters in a population attempting to mimic REDUCE-IT.[23] The study was criticised by the ERG as it is not possible to clearly attribute changes in biochemical parameters to the placebo oil, rather than differences in patient characteristics. In summary, we see no scientific plausibility to model a reduction in treatment effect for icosapent ethyl in the range 7-13%. Amarin has performed scenario analyses to investigate how a hypothetical worst case 0.3-3% reduction in the treatment effect for icosapent ethyl, as specified by the regulatory authorities, would impact the ICER. The results are presented in Table 3. The professional group and NHS England clinical adviser also commented that results of a *'similar trial'*, STRENGTH, did not show the same magnitude of benefit as REDUCE-IT.[24] Amarin would like to draw the Committee's attention to key differences between the STRENGTH and the REDUCE-IT trials including significant differences in the investigational medicinal product tested (REDUCE-IT, 4 g/ day of ≥96% pure EPA ethyl ester vs. STRENGTH, 4 g/ day of omega-3-carboxylic acids with at least 850 mg of polyunsaturated fatty acids, including multiple omega-3 fatty acids, EPA and DHA being the most abundant), and the population studied (REDUCE-IT secondary prevention group 70.7% vs. 55.6% in STRENGTH).[25] The Committee for Medicinal Products for Human Use (CHMP) has concluded that *"….icosapent ethyl is considered to be a new active substance as it differs significantly in properties with regard to efficacy from EPA and mixtures of constituents contained in medicinal product(s) previously authorised within the European Union ("omega-3-acid ethyl esters 90")."*[8] The biological activity of highly-purified EPA ethyl ester in REDUCE-IT is further supported by significant reductions in CV events observed in the JELIS trial, with additional benefits on reducing coronary atherosclerotic plaque volume in the EVAPORATE trial.[26,27]
6	**Low rate of eructation / unpleasant burps with icosapent ethyl**

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	In Section 3.9 of the ACD, the following was stated: '*The committee noted that some fish oil products can be associated with unpleasant burps that may affect adherence'*. In the REDUCE-IT trial, only [redacted] of patients in the icosapent ethyl arm and [redacted] of patients in the placebo arm experienced eructation.[28] Furthermore, only [redacted] patients in the icosapent arm withdrew from the study drug due to experiencing eructation, compared to [redacted] patients in the placebo arm.[28] This shows that unpleasant burps experienced by patients have very little impact on treatment adherence. Overall, the European Medicines Agency considered that the safety profile of icosapent ethyl was relatively benign.[8]
7	**Model structure** To align with what is observed in the REDUCE-IT trial, time-to-event endpoints were modelled so that individuals are solely able to progress in a specific order through health states, for example, unable to skip or return to a previous state. Over the trial period, it would not be possible for an individual to experience a second event prior to a first event. The model uses the time from randomisation to a first, second or third plus event, therefore there would be no issues surrounding a crossover of the first, second of third plus event endpoints reported during the trial period. Beyond the trial period, extrapolations were used for the first, second and third plus event curves. Any curves that crossed over the previous event curve were disregarded and considered clinically implausible. Amarin are not aware of any external UK datasets that could be used to estimate the baseline risk, therefore the placebo arm of the REDUCE-IT trial was used.
8	**A similar trend in results is observed for each individual component of the 5-point MACE** In Section 3.11 of the ACD, it was noted that: "*The committee concluded the composite 5-point MACE outcome increases uncertainty and it would like to see the Kaplan–Meier curves and hazard ratios for each of the individual cardiovascular events."* To address the ERG's concern that the 5-point composite MACE may mask the treatment effect on individual CV events, Kaplan-Meier curves and hazard ratios for each event type have been provided for the secondary prevention cohort. In the REDUCE-IT trial, icosapent ethyl treatment demonstrated a decreased incidence rate of each of the individual endpoints included in the 5-point MACE compared to placebo, and this benefit was sustained over the study period for each event. The hazard ratios for CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, and unstable angina were

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	[redacted], respectively. The hazard ratio for the primary composite endpoint was [redacted] (Figure 4). Kaplan-Meier curves for each treatment arm showing the proportion of patients that have experienced each CV outcome included in the 5-point MACE are presented in Figure 4 to Figure 9. Hazard ratios for each outcome over the course of the trial following randomisation are presented in Figure 10 to **Figure 14**.
9	**Full time to event analysis is provided for the secondary prevention subgroup and validated by UK clinical experts as well as against an external validation model** In Section 3.12 of the ACD, it was noted that: *"The ERG noted that the time to event analysis was only provided for the intention to treat population and not for the primary and secondary prevention subgroups. It also noted that different parametric curves might be more suitable for the subgroup analyses"* To inform the new base case based on the secondary prevention cohort, a full time to event analysis is provided below and includes: • A write-up of the methodology adopted to inform time-to-event modelling in the secondary prevention cohort within the cost-effectiveness model • Clinical validation for the selected time-to-event curves for the secondary prevention cohort • Clinical validation of the overall survival estimates from the cost-effectiveness model • Comparison of overall survival from REDUCE IT and overall survival observed in the cost-effectiveness model • Comparison of the Company model outcomes with the external validation model

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	In line with NICE DSU 14, full details of the methodology used for estimating the long-term time-to-event curves for first, second and third plus events for the secondary prevention cohort applied within the cost-effectiveness model are presented below.[29] ***Assessment of proportional hazards assumption*** To test for the acceptability of using proportional hazards, the log cumulative hazard plot, Schoenfeld residual plot and Cox-Snell residual plots were evaluated (Figure 16, Figure 17 and Figure 18, respectively, in the appendix presenting the new evidence). The log-cumulative hazard plot lines for icosapent ethyl and placebo remain parallel for the majority of the time period in all three events. However, the plot lines do cross towards the start in the first and second event and towards the end of the third plus event. This could be due to the treatment not showing full effect at the beginning of the time period and few patients remaining at risk towards the end of the time period. The Schoenfeld residual plot shows a linear curve with a zero slope for events one and two and, shows a p value >0.05 for all events, giving evidence that the proportional hazards assumption holds. The plot of the Cox-Snell residuals against the estimated cumulative hazard rate shows a relatively straight line with zero intercept and unit slope for event one. Due to there being a small number of patients experiencing a second or third plus event, large jumps are observed in the plot at later time points for the second event and third plus events. It can be assumed that the proportional hazards assumption holds between icosapent ethyl and placebo. Therefore, based on these findings and the algorithm in Figure 19 in NICE DSU14, dependent fitted extrapolation models were deemed most appropriate to extrapolate the first, second and third plus time-to-event curves for the secondary prevention population.[29] ***Selection of survival curves*** The six standard survival models (Exponential, Weibull, Gompertz, log-logistic, log-normal and Generalised Gamma) were fitted to the placebo and icosapent ethyl arms simultaneously, with a covariate for the icosapent ethyl group included (see Figure 20 to Figure 25 in the appendix presenting the new evidence). In relation to the following statement in the ACD: *"The ERG did highlight that the model allowed different curves to be selected for each treatment group, suggesting that it was not a jointly modelled approach."* Amarin would like to clarify that the placebo and icosapent ethyl arms were fitted simultaneously using dependant survival analysis in the current company base case, meaning that the same distribution should be selected for both treatment groups within the model. The functionality available in the cost-effectiveness model to use different curve distributions is only applicable if independent survival analysis is being used.

	When the survival analysis was conducted using the ITT population, the Weibull distribution caused an error, and we were unable to obtain parameter coefficients. The analysis was conducted again using only the secondary prevention population and there was no error with fitting the Weibull distribution to the data. The best fitting distribution was chosen by statistical consideration (AIC and BIC) and visual inspection of the fitted curves against the Kaplan Meier data to ensure the survival distributions closely predicted the observed data. Additionally, comparison of outcomes against the external [redacted] cost-effectiveness model adapted to a UK perspective (further details regarding the methodology applied in the external validation model are available in Weintraub *et al.* 2022 from a US healthcare perspective[9]) and clinical plausibility of the long-term extrapolations as assessed by three UK clinical experts, were considered. Lower AIC and BIC values are associated with better statistical fit to the observed data. Therefore, based on statistical fit, the most appropriate distributions to be used for the time-to-event curves were determined to be Exponential, log-logistic and log-logistic, for the first event, second event and third plus event, respectively. In general, most of the parametric models fitted well to the data and produced reasonable visual predictions for placebo and icosapent ethyl within the observed period. A summary of the goodness-of-fit statistics for the first, second and third plus event extrapolations are presented in Table 4. Table 5, Table 6 and Table 7 present a 30-year time horizon comparison against the estimates provided from the [redacted] model, for the first, second and third plus event curves, respectively. For the first event curve, the Exponential distribution (best fitting chosen by statistical consideration) was very similar to the percentage of individuals experiencing the primary endpoint as reported in the Kaplan Meier curve reported in the REDUCE-IT trial CSR. Additionally, over a time horizon of 30 years, the estimates are similar to those observed in the [redacted] cost-effectiveness model. There is still some uncertainty surrounding the second and third plus event curve distributions to inform the long-term estimates, with the best fitting curve chosen by statistical consideration being the one based on the log-logistic distribution, while the curve based on the exponential distribution results in estimates closer to those observed in the [redacted] model (Kaplan Meier curves were not generated separately for second events and third plus events). However, scenario analyses presented in Table 8, Table 9 and Table

	10, show that the choice of distribution for the second and third plus events has minimal impact on the ICER.
	
	Clinical plausibility of model assumptions and inputs including time-to-event long-term extrapolations were validated by three UK clinical experts. The experts used to derive the expert opinion to support assumptions and decisions made with regard to the economic model were:
	
	• **Expert 1:** Professor of Public Heath in the Department of Public Health and Primary Care at Imperial College London as well as Honorary Consultant Cardiologist at the Imperial College NHS Trust.
	  o Research interests have focused on the prevention of cardiovascular disease with a special interest in lipids and diabetes.
	  o His work has influenced American Heart Association/American College of Cardiology and European Society of Cardiology guidelines
	• **Expert 2:** Honorary Senior Research Fellow at the Institute of Cardiovascular and Medical Sciences at the University of Glasgow.
	  o Over his career he has focussed on two aspects of atherosclerosis research, lipoprotein metabolism and how it is affected by diets and drugs, and large-scale clinical trials of lipid lowering agents.
	  o Study director and one of the main investigators of the West of Scotland Coronary Prevention Study (WOSCOPS) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER).
	• **Expert 3:** Consultant interventional cardiologist and honorary senior clinical lecturer.
	  o Chief or primary investigator of multiple large trials in Cardiovascular medicine.
	  o Developed one of the UK's first primary angioplasty programmes, and one of the UKs largest cardiac CT programmes.
	
	All three UK clinical experts believed that the range of estimates produced from the updated time-to-event analyses were similar to what they would expect to observe in UK clinical practice. As the estimates produced by each of the parametric curves were similar, the clinical experts recommended selecting the best fitting curve (assessed using AIC and BIC values) in the base case.
	
	Further noted in Section 3.12 of the ACD:
	
	"This should include a comparison of model-predicted overall survival compared with overall survival in REDUCE-IT. This should also consider clinical expert judgements on the plausibility of the long-term model predictions (…) for overall survival."

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	Table 11 provides a comparison of overall mortality from the REDUCE-IT trial to overall mortality estimated from the company cost-effectiveness model. Some discrepancies were noted between the model and REDUCE-IT trial in terms of overall mortality, therefore the company investigated further the cause of these discrepancies. The company concluded that background mortality should be adjusted to only take into account non-CV related UK general mortality, in order to avoid double counting of CV related mortality. Hence, background mortality has been adjusted in the model to remove CV related mortality. Life tables reporting all-cause mortality by age and sex in the UK were obtained from the Office for National Statistics (ONS) and were converted to mortality rates.[30] The ICD-10 codes associated with CVD (Table 12) were identified, and corresponding mortality rates from the World Health Organisation (WHO) were totalled for each age group and sex to give CV-specific mortality rates per 100,000 population (Table 13).[31] The CV-specific mortality rates were subtracted from the all-cause mortality rate life tables and converted back to probabilities to give non-CV mortality probabilities stratified by age and sex (Table 14). Amarin sought clinical expert opinion for the clinical plausibility of the survival rates for the placebo group at 1, 5, 10, 20 and 30 years, as well as the estimated age of death taken from the cost-effectiveness model applying the new company base case assumptions (including adjusted non-CV background mortality). All three UK clinical experts believed that the survival estimates produced from the model were similar to what they would expect to observe in UK clinical practice. Amarin believe the remaining discrepancies between the overall mortality in the REDUCE-IT trial and the cost-effectiveness model are likely attributed to the controlled environment of a clinical trial setting. This rationale was also supported by the UK clinical experts consulted, who highlighted that clinical trials generally tend to recruit "healthier" patients, resulting in lower mortality rates observed in clinical trials compared to patients in the real world.
10	**The evidence and expert input available do not support the application of a treatment waning effect** In Section 3.13 of the ACD, it was noted that: *"The committee … was concerned that treatment discontinuation was not linked to treatment effect in the icosapent ethyl model(…) The committee concluded it would have preferred a method linking treatment effect and discontinuation by changing the hazard ratio to 1 at an appropriate time after people stopped icosapent ethyl."* Whilst Amarin acknowledge the Committee's concerns regarding treatment discontinuation not being linked to treatment effect in the cost-effectiveness model, efficacy data applied within the model is based on the REDUCE-IT

	trial intention-to-treat analysis. As such, outcomes include the clinical efficacy for all patients randomised to icosapent ethyl regardless of whether they discontinued icosapent ethyl within the trial period. Including all patients that were randomised to icosapent ethyl means that within the clinical efficacy curves estimated, any efficacy lost due to discontinuation is accounted for. Additionally, as discussed in the company's technical engagement response, although patients discontinued treatment during the REDUCE-IT trial, the Kaplan-Meier event curves for the primary efficacy 5-point MACE composite endpoint (Figure 5 in the company submission), showed that the treatment effect increases over time before stabilising. [redacted] [redacted] Despite the absence of long-term studies to inform whether or not the treatment effect is maintained, no waning was applied in the appraisals of alirocumab TA393, evolucumab TA394 and inclisiran TA733, which are in a similar disease area (hypercholesterolaemia and mixed dyslipidaemia).[10–12] Finally, as noted by a clinical expert in the ACD, '*related treatments for cardiovascular disease, such as statins, have long term effects.* In his response to the technical engagement, a clinical expert commented that *'the company's assumption of no waning was likely reasonable*.' As a result, any treatment waning scenario applied is likely to be an underestimate of the efficacy observed in those who stop treatment. Amarin believe it is reasonable to assume that the treatment benefit of icosapent ethyl would be maintained beyond the trial period, and therefore no treatment waning should be applied in the base-case. In scenario analyses only, Amarin has implemented treatment waning to patients who discontinue icosapent ethyl following the trial period: • In a first scenario, it is assumed that once a patient discontinues, after an arbitrary period of 20 years, they will have equal clinical efficacy to those in the placebo group (treatment coefficient=0).

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	• In a second scenario, it is assumed that once a patient discontinues, after an arbitrary period of 10 years, they will have equal clinical efficacy to those in the placebo group (treatment coefficient=0). There is an important caveat when modelling these scenarios in that the icosapent ethyl evidence base is supportive of preventing CV events, not delaying CV events. When assuming patients who discontinue follow the clinical efficacy of those in the placebo treatment group (treatment coefficient=0), it is assuming that all those events that were avoided suddenly occur on discontinuation, which is not reflective of what would actually happen to an individual in reality. Clinical experts consulted by Amarin agree that the clinical plausibility of these scenarios is questionable.
11	**Full analysis for time to treatment discontinuation (TTD)** In section 3.13 of the ACD, it was noted: *'The committee would have liked to see the full analysis for time to treatment discontinuation, including for subgroups."* A summary of the analysis for TTD for the secondary prevention cohort is presented below. Survival models were fitted to the full patient-level data for TTD for the secondary prevention subgroup within the REDUCE-IT trial, as recommended in NICE DSU14 guidance.[29] Extrapolations were carried out in R using the 'survival' package. For all the curves, the following criteria were applied to select the baseline curves: • Statistical model fit, as measured by AIC and BIC • Visual inspection of the survival curve fitted to the Kaplan-Meier data from the REDUCE-IT trial Exponential, Weibull, Gompertz, log-logistic, lognormal, and Generalised Gamma were assessed for statistical goodness-of-fit by the AIC and BIC criteria. The Weibull distribution had the lowest AIC and BIC, indicating that this was the best fit to the observed data (Table 16). This was consistent with the visual assessment of goodness-of-fit, as presented in **Error! Reference source not found.**. The analysis for each distribution is summarised in Figure 26. Scenario analyses were conducted to explore the impact of using different distributions (Table 17).
12	**Evidence that diabetes and number of previous events are non-CV related death modifiers** In Section 3.14 of the ACD, it was noted that: *"The committee concluded the non-cardiovascular-related death hazard ratios are uncertain and it would like to see evidence that diabetes and number of previous events are non-cardiovascular-related death modifiers."*

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	Three UK clinical experts consulted following the first appraisal committee meeting agreed that both a history of diabetes and previous CV events would be considered non-CV related death modifiers. They highlighted that individuals diagnosed with diabetes are associated with substantial premature death from several cancers, infectious diseases, external causes, intentional self-harm, and degenerative disorders, independent of several major risk factors.[13] Furthermore, those who have previously experienced CV events such as a stroke are at an increased risk of respiratory infections, which could again lead to premature death. The effects of prior CV events on non-CV related death has been investigated in the literature, and has shown that reducing total nonfatal CV events has a statistically significant effect on non-CV related deaths.[14] There are also several other studies that have demonstrated an association between increased non-CV related mortality and a history of diabetes or previous CV events. The relevant findings of these studies are summarised below: • In a retrospective comparison of mortality in 963,648 diabetic and non-diabetic individuals, the incidence of all-cause mortality was increased in individuals with diabetes compared to those without diabetes. Diabetic participants had an increase of 7 deaths per 1000-person-years compared to non-diabetic participants, of which 3.5 deaths per 1000-person-years were attributable to CVD, suggesting 3.5 additional non-CV disease related deaths per 1000-person-years were observed in the diabetes group compared to the non-diabetes group.[32] • A survey of 15,513 participants found that diabetes contributed to increased chance of mortality due to a variety of non-CV related causes. In diabetic participants, hazard ratios (adjusted for sex, age, body mass index, smoking status, and alcohol-use status) for mortality due to cancer, chronic lower respiratory diseases, cerebrovascular disease, flu/pneumonia, and kidney disease were 1.08, 1.58, 1.54, 3.56 and 3.00, respectively when compared to the general population.[33] • An epidemiological analysis involving 313,907 individuals with diabetes showed increased mortality rates for a variety of non-CV diseases compared to non-diabetic individuals. In diabetic men, mortality rates per 1000-person-years for cancer, renal disease, liver disease, respiratory disease and dementia were 9.3, 0.2, 0.7, 4.0 and 3.8 respectively, compared to 4.8, 0.1, 0.3, 2.2 and 1.8 in non-diabetic men. In diabetic women, mortality rates per 1000-person-years for cancer, renal disease, liver disease, and dementia were 8.1, 0.2, 0.5 and 6.6 respectively, compared to 4.2, 0.1, 0.2, and 3.9 in non-diabetic women.[34] • In an epidemiological study of 62,785 individuals, diabetic participants were found to have an increased hazard ratio (adjusted for age, sex, worksite, BMI, smoking status, hypertension, and dyslipidaemia) for non-CVD related and non-cancer related mortality

	compared to non-diabetic participants. The adjusted hazard ratio for diabetic individuals was 2.44.[35] • A 10-year longitudinal study compared all-cause mortality before and after coronary heart disease or stroke in 10,424 individuals and showed that mortality was increased following both CV events. All-cause mortality prior to coronary heart disease or stroke was 5.91 per 1000-person-years, and 15.58 and 34.52 per 1000-person-years following coronary heart disease and stroke, respectively.[36] • In a study of 3,092,580 individuals measuring mortality risk following incident myocardial infarction or new-onset diabetes over the course of 5 years post-event, relative all-cause mortality risk ranged from 1.38 to 8.67 following myocardial infarction and 1.42 to 2.51 following diabetes compared to the background population.[37] • In a 10-year study of 1,024 patients with coronary heart disease, age-adjusted hazard ratios for non-CV mortality in patients with heart failure, stroke, diabetes or myocardial infarction were 1.47, 1.29, 1.76 and 1.35, respectively.[38] • Risk of mortality due to non-CV causes was found to be increased in patients following a first stroke event in an analysis of 4,162 stroke patients. Standardised mortality ratios for cancer, other non-CV diseases and accidents/suicide in men were 1.22, 2.20 and 1.88, respectively, and 1.33, 1.83 and 1.82, respectively in women compared to the general population.[39]
13	**The company's model has been further validated with an external model developed for icosapent ethyl** In Section 3.15 of the ACD: *"The ERG noted that additional details on the discrepancies in the original cross validation and explanation for the remaining differences in the updated cross validation would be helpful."(….)* "The committee concluded that there were unresolved uncertainties in the company's model that should be addressed before comparison with the validation model." A state-transition model in TreeAge, developed by the [redacted] group[9], has been provided to validate the outcomes of the company's partSA approach. The objective of the state-transition model was to estimate the cost-effectiveness of icosapent ethyl compared with standard of care, using patient-level data from REDUCE-IT for the in-trial period, and using a microsimulation model and data from published literature for the lifetime analysis. At the technical engagement stage, it was noted that there was a discrepancy in the way the proportion of patients experiencing each type of event were calculated for the cross-validation model. Rather than calculating the proportions based on the total cohort entering the model, the proportions were calculated based on the number of patients left in the model each year. This was corrected, and an update of the estimates was provided to NICE on

	20th December 2021, which showed that the values across both models were more consistent. Please note that there are still some discrepancies between the clinical outcomes of both models due to the following reasons: • The extrapolation curves for the partSA model have been selected based on best fit. Table 5 to Table 7 demonstrate the impact that the curve choice has on the long-term clinical outcomes, and how this compares with the cross-validation model. • The partSA model uses survival curves based on the REDUCE-IT trial data to estimate long-term clinical extrapolations, whereas the cross-validation model uses transition probabilities adjusted by age and sex. • The cross-validation model only included the costliest event when multiple events occurred within a three-day period, whereas the partSA model was able to factor all these events in due to the shorter cycle length (daily cycles). • Different sources for background mortality were used, and the mortality estimates in the partSA model were adjusted to avoid double counting of CV-related death. • Different sources were used for the baseline utility values. • Acute utilities were applied for 60 days in the partSA model but were applied for 18 months in the cross-validation model. • The partSA model estimated utility values using multipliers from NICE CG181, whereas the cross-validation model applied utility decrements based on the type of event experienced by patients. • Acute costs were applied for 60 days in the partSA model but were applied for 18 months in the cross-validation model. • The partSA model only considered adverse events which occurred in >5% of individuals that were significant in the icosapent ethyl group, whereas the cross-validation model considered all adverse events from the REDUCE-IT trial. During the ACD consultation period, a new comparison, focusing on the secondary prevention cohort only, has been undertaken between the company model and the cross-validation model. The updated comparison of clinical outcomes can be found in Table 18**Error! Reference source not found.**. Table 19 compares the results of the state-transition model and the partSA model. Despite the discrepancies listed above, the results are very similar between the partSA and cross-validation models, demonstrating the robustness of the partSA approach used compared to a conventional Markov

	approach. The incremental costs, life years, and quality-adjusted life years are all very similar, which results in very similar ICERs.
14	**Revised economic analyses for the subgroup of patients in secondary prevention:** We have considered recommendations from the ERG and have revised our base case in the cost-effectiveness model, to include the following assumptions: • Secondary prevention population only • Independent HRs to inform non-CV related mortality, in line with the ERGs recommendation • Weibull distribution to inform the time-to-treatment discontinuation curve, based on best statistical fit in the secondary prevention population • Background mortality adjusted to solely include non-CV related mortality • List price reduced from £173 to £[redacted] per pack of 120 capsules The revised company base case results in an ICER of £19,848 (presented in Table 20 in the additional information appendix). The revised probabilistic sensitivity analysis (PSA) results of icosapent ethyl versus placebo are presented in Table 21. The PSA was ran for 5,000 iterations and the results are similar to those of the deterministic base-case (Table 20). Patients receiving icosapent ethyl accrued 8.099 QALYs at a cost of £23,470. Patients receiving placebo accrued 7.636 QALYs at a cost of £14,373, respectively. This resulted in a mean PSA ICER of £19,625. The incremental cost-effectiveness plane (ICEP) in Figure 28 shows that most of the iterations fell in the north-east quadrant, where icosapent ethyl is more costly but more effective than placebo. The cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) are presented in Figure 29 and Figure 30, respectively. A tornado diagram is presented in Figure 31 for icosapent ethyl versus placebo to illustrate the level of uncertainty around the ICER via a one-way sensitivity analysis (OWSA). The top 20 most sensitive parameters and the associated results are presented in tabular format in Table 22. The OWSA results demonstrated the model was most sensitive to the baseline utility value of the secondary prevention population and the treatment cost for icosapent ethyl. All scenarios discussed in sections 1-13 of this document are investigating the impact of alternative assumptions on the company revised base case as detailed below. In addition, scenario analyses were conducted varying the key parameters where uncertainty has been raised in the ACD: o Relative reduction in treatment benefit

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	o Treatment waning o Time-to-event distributions selection in curves o Time-to-treatment discontinuation selection in curve

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New evidence

Generalisability of the REDUCE-IT trial results to the NHS in England

Table 1: Comparison of CV risk in REDUCE-IT trial and other studies in similar target populations

	REDUCE-IT (N=5,785)	Steen *et al.*[4] (N=91,497)	Lawler *et al.*[5] (N=196,717)	Ferrieres, J *et al.* (N=472)
Demographic characteristics				
Age (years), Mean	[redacted]	72.6	66.0	61.0
Male, %	[redacted]	60.7	69.9	79.4
BMI (kg/m^2), Mean	[redacted]	28.3	NR	NR
Systolic BP, Mean	[redacted]	132.1	NR	
Disease-relevant baseline characteristics				
Recent ACS, %	[redacted]	3.4	49.9	100.0
Other CHD, %	[redacted]	66.0	37.2	NR
Ischaemic stroke/TIA, %	[redacted]	28.6	10.0	NR
PAD, %	[redacted]	21.7	8.0	NR
DM, %	[redacted]	29.4	44.5	29.4
Hypertension, %	[redacted]	61.5	82.6	56.5
History of CHF, %	[redacted]	9.1	12.1	17.4
CKD, stage III, %	[redacted]	23.5	NR	NR
CKD, stage IV-V, %	[redacted]	0.2	NR	NR
Statin Intensity				
Low-intensity statin, %	[redacted]	5.6	NR	2.3
Medium-intensity statin, %	[redacted]	42.1	NR	32.2
High-intensity statin, %	[redacted]	31.4	NR	65.5
Overall statin use, %			95.5	100.0
Medications taken at baseline				
Anti-Platelet, %	[redacted]	18.5	NR	96.4
ACE or ARB, %	[redacted]	61.7	NR	93.9
Beta Blockers, %	[redacted]	48.7	NR	86.7

Abbreviations: ACE – Angiotensin-converting enzyme inhibitor; ACS – Acute coronary syndrome; ARB – Angiotensin II receptor blocker; BMI – Body mass index; CHF – Congestive heart failure; CKD – Chronic kidney disease DM – Diabetes mellitus; PAD – Peripheral arterial disease; TIA – Transient ischaemic attack

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Mineral oil placebo in REDUCE-IT

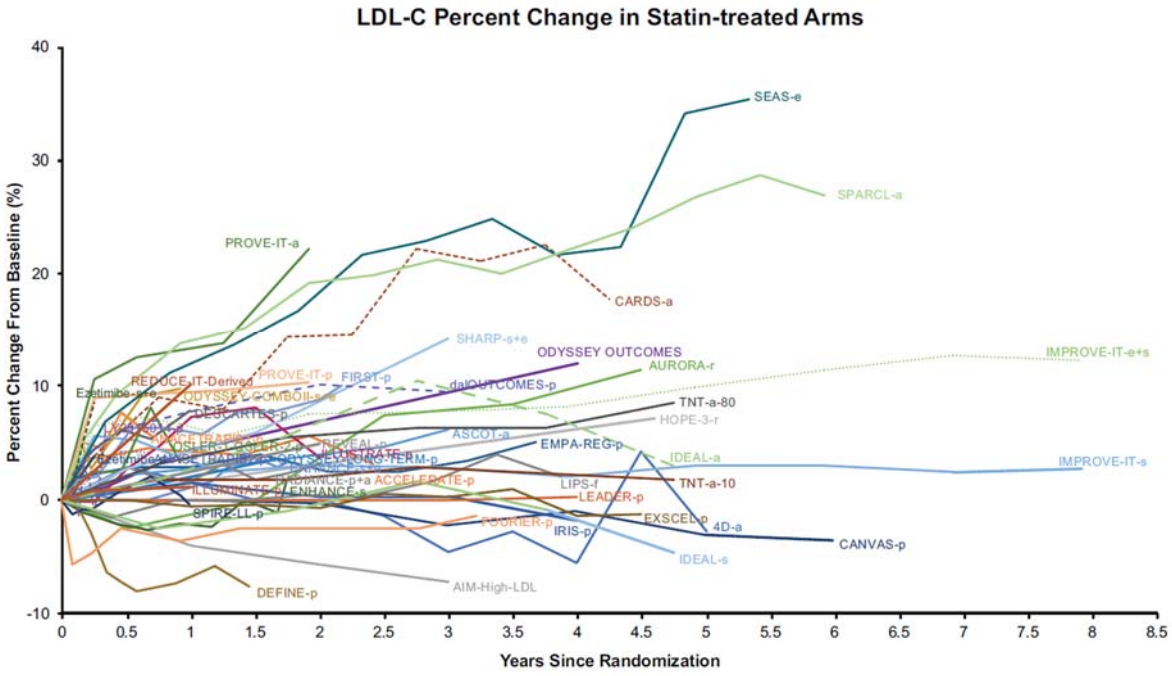
Table 2. Laboratory parameters at baseline and 1 year

	Icosapent ethyl			Placebo		
	Baseline	1 Year	Median Change	Baseline	1 Year	Median Change
Triglycerides, mg/dL	216.5	[redacted]	[redacted]	216.0	[redacted]	[redacted]
Non-HDL-C, mg/dL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDL-C, mg/dL	74.0	[redacted]	[redacted]	76.0	[redacted]	[redacted]
apoB, mg/dL*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP, mg/L*	2.2	[redacted]	[redacted]	2.1	[redacted]	[redacted]

*Baseline to Year 2

Abbreviations: apoB – Apolipoprotein B; HDL-C – High-density lipoprotein cholesterol; hsCRP – High-sensitivity C-reactive protein; LDL-C – Low-density lipoprotein cholesterol

Figure 1. LDL-C percent change in statin-treated arms



Adapted from Olshansky, B et al. European Heart Journal Supplements (2020) 22 (Supplement J), J34–J48.[22] Overview of the low-density lipoprotein cholesterol (LDL-C) percentage changes observed in statin-treated cohorts from recent (published since 2003) CV outcome trials and other long-term studies that reported at least two statin-treated low-density lipoprotein cholesterol measurements over time.

Figure 2. Time to primary endpoint by change in hsCRP at 2 years

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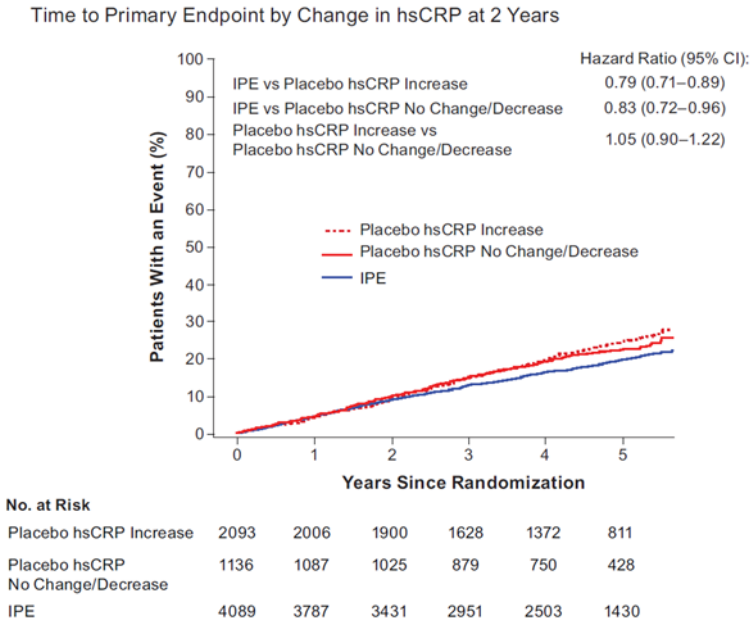
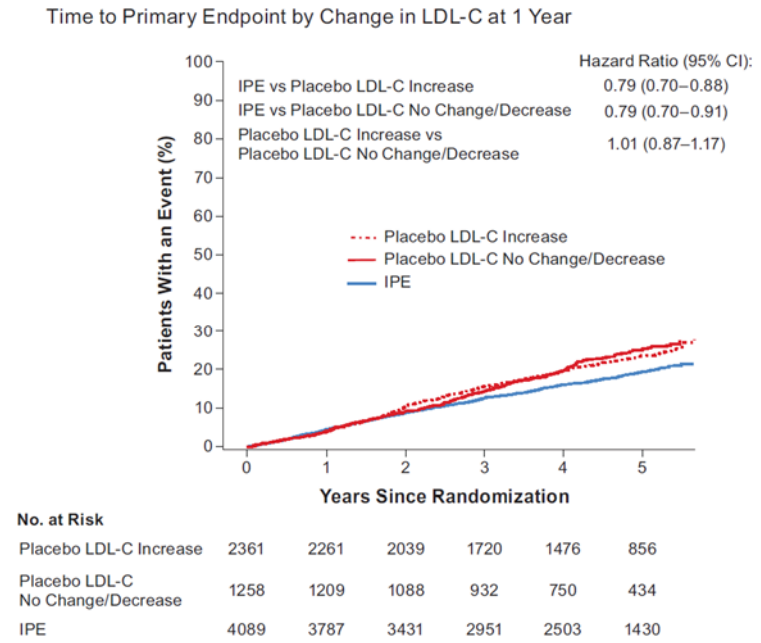


Abbreviations: CI – confidence interval; hsCRP – High-sensitivity C-reactive protein; IPE – Icosapent ethyl
Adapted from Olshansky, B et al. European Heart Journal Supplements (2020) 22 (Supplement J), J34–J48.[22]

Figure 3. Time to primary endpoint by change in LDL-C at 1 year



Abbreviations: CI – confidence interval; IPE – Icosapent ethyl; LDL-C – Low-density lipoprotein cholesterol
Adapted from Olshansky, B et al. European Heart Journal Supplements (2020) 22 (Supplement J), J34–J48.[22]

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Table 3. Hypothetical scenario analyses varying reduction in treatment effect

Reduction in treatment effect	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case (no reduction)	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	9,723	0.385	0.490	19,848
0.3%	Placebo	13,938	11.206	7.877	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	9,755	0.380	0.484	20,157
1%	Placebo	13,863	11.219	7.891	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	9,830	0.368	0.470	20,908
2%	Placebo	13,757	11.236	7.911	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	9,937	0.350	0.450	22,063
3%	Placebo	13,650	11.254	7.931	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	10,044	0.333	0.431	23,325

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years.

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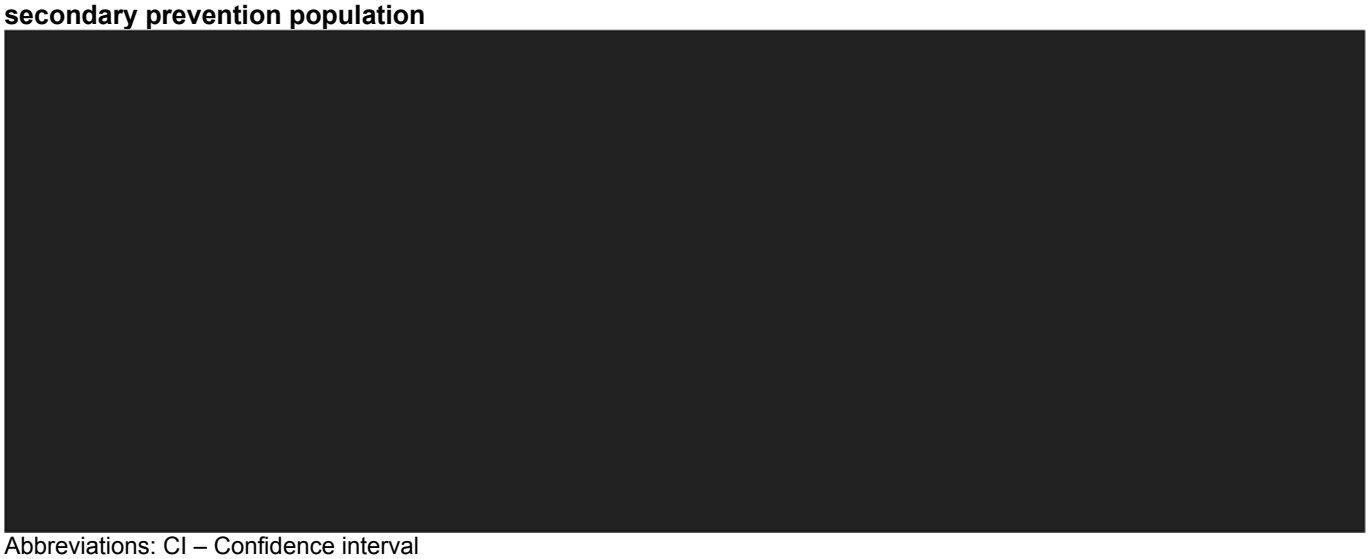
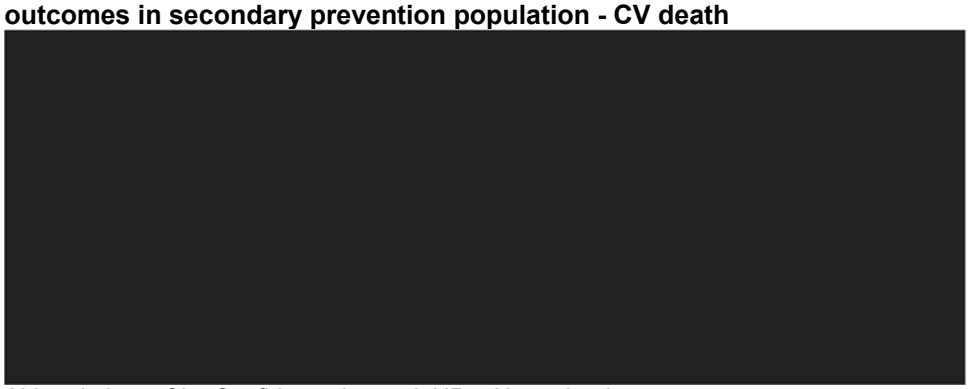
A similar trend in results for the 5-point MACE is observed for each individual component of the 5-point MACE

Figure 4: Forest plot showing hazard ratios for the individual components of the 5-point MACE in secondary prevention population



Abbreviations: CI – Confidence interval

Figure 5: Kaplan-Meier distributions showing proportion of patients that have experienced individual CV outcomes in secondary prevention population - CV death



Abbreviations: CI – Confidence interval; HR – Hazard ratio

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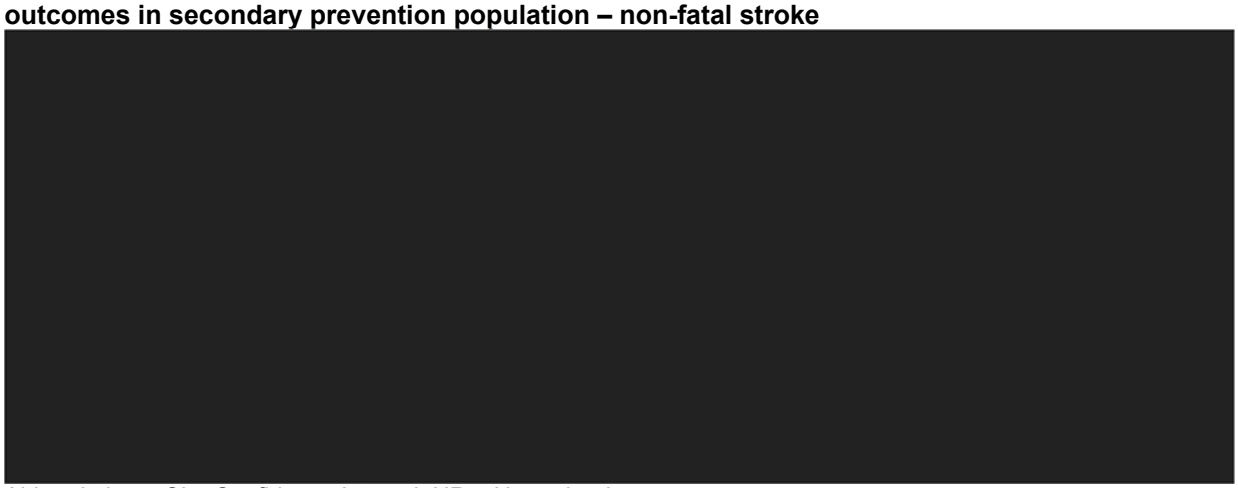
Figure 6. Kaplan-Meier distributions showing proportion of patients that have experienced individual CV outcomes in secondary prevention population – non-fatal MI

Abbreviations: CI – Confidence interval; HR – Hazard ratio

Figure 7: Kaplan-Meier distributions showing proportion of patients that have experienced individual CV outcomes in secondary prevention population – non-fatal stroke



Abbreviations: CI – Confidence interval; HR – Hazard ratio

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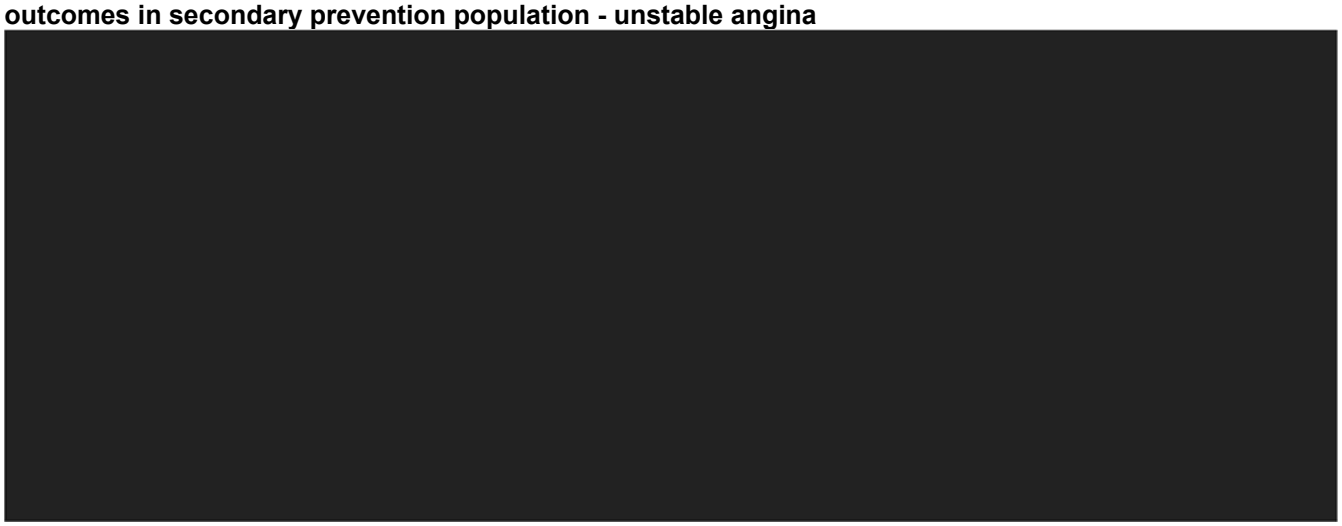
Figure 8. Kaplan-Meier distributions showing proportion of patients that have experienced individual CV outcomes in secondary prevention population - coronary revascularisation

Abbreviations: CI – Confidence interval; HR – Hazard ratio

Figure 9: Kaplan-Meier distributions showing proportion of patients that have experienced individual CV outcomes in secondary prevention population - unstable angina



Abbreviations: CI – Confidence interval; HR – Hazard ratio

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Figure 10: Kaplan-Meier distributions showing proportion of patients that have experienced primary endpoint in secondary prevention population – 5-point MACE

Abbreviations: CI – Confidence interval

Figure 11: Hazard ratios over time for each individual CV outcome in secondary prevention population - CV Death

Abbreviations: CI – Confidence interval; HR – Hazard ratio

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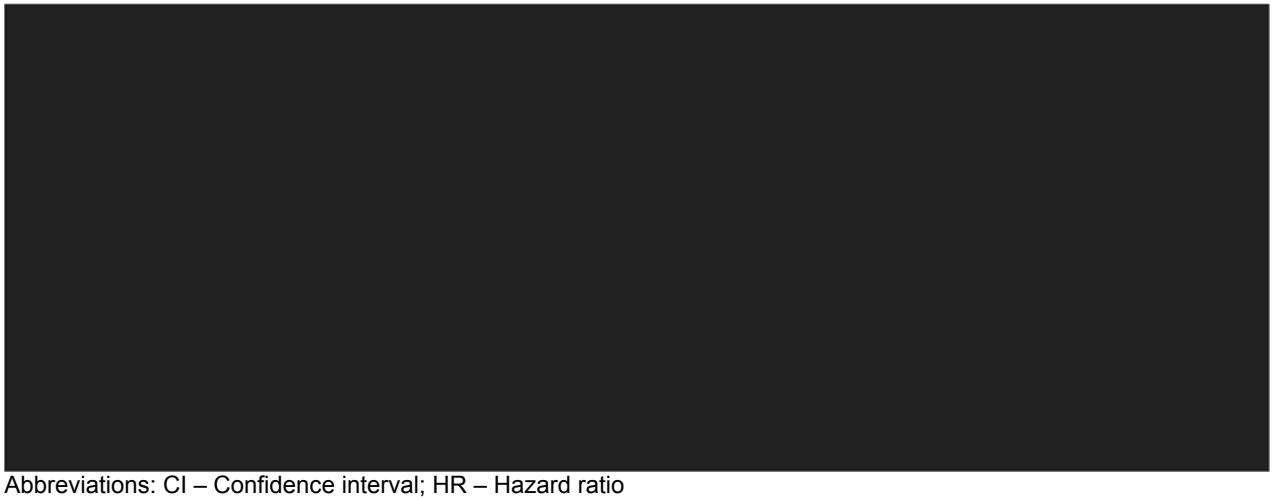
Figure 12: Hazard ratios over time for each individual CV outcome in secondary prevention population – non-fatal MI

Abbreviations: CI – Confidence interval; HR – Hazard ratio

Figure 13: Hazard ratios over time for each individual CV outcome in secondary prevention population – non-fatal stroke



Abbreviations: CI – Confidence interval; HR – Hazard ratio

Figure 14: Hazard ratios over time for each individual CV outcome in secondary prevention population – coronary revascularisation

Abbreviations: CI – Confidence interval; HR – Hazard ratio

Figure 15: Hazard ratios over time for each individual CV outcome in secondary prevention population – unstable angina

Abbreviations: CI – Confidence interval; HR – Hazard ratio

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Full time to event analysis is provided for the secondary prevention subgroup and validated by UK clinical experts as well as against an external validation model

Assessment of proportional hazards assumption

Figure 16: Log cumulative hazard plots for the secondary prevention population

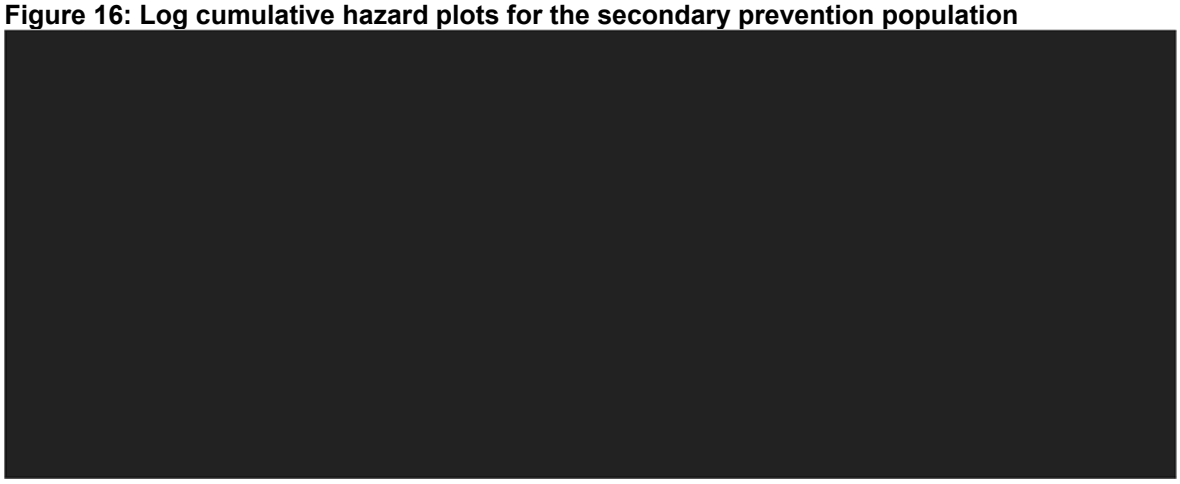

Figure 17: Schoenfeld residual plots for the secondary prevention population

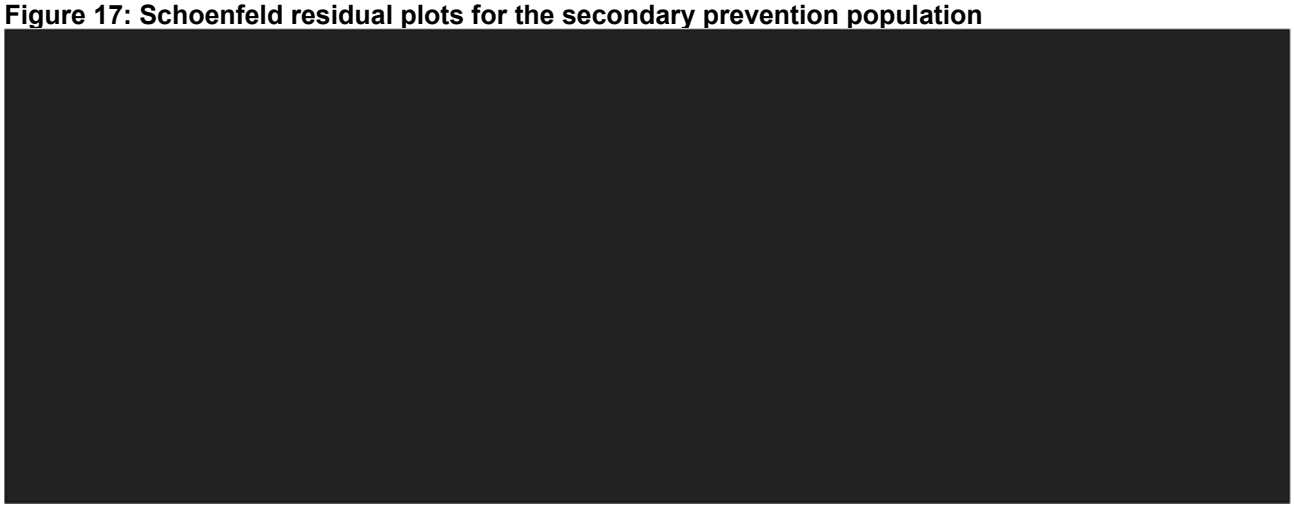

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Figure 18. Cox-Snell plots for the secondary prevention population

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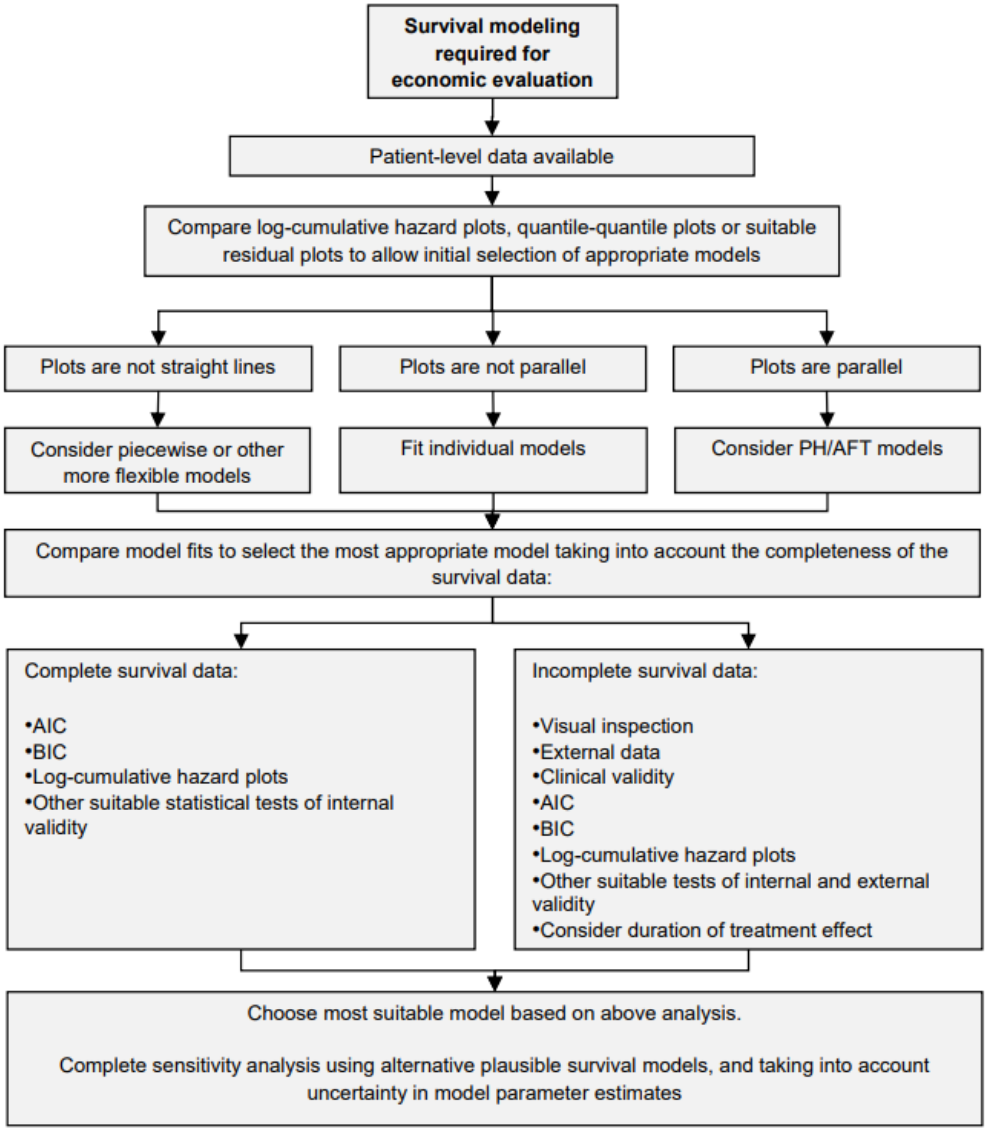
Figure 19. Survival Model Selection Process Algorithm



Abbreviations: AFT – Accelerated failure time; AIC – Akaike information criterion; BIC – Bayesian information criterion; PH – Proportional hazards

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Selection of survival curves

Figure 20: Long-term extrapolations for first event (dependant models): secondary prevention population (Icosapent ethyl)

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier

Figure 21: Long-term extrapolations for first event (dependant models): secondary prevention population (Placebo)

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier

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Figure 22: Long-term extrapolations for second event (dependant models): secondary prevention population (Icosapent Ethyl)

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier

Figure 23: Long-term extrapolations for second event (dependant models): secondary prevention population (Placebo)

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier

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Figure 24: Long-term extrapolations for third plus event (dependant models): secondary prevention population (Icosapent Ethyl)

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier

Figure 25: Long-term extrapolations for third plus event (dependant models): secondary prevention population (Placebo)

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier

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Table 4. Goodness-of-fit statistics for the secondary prevention population

Distribution	AIC	Rank	BIC	Rank	Diff rank
First event					
Exponential	***25190***	***2***	***25204***	***1***	***1***
Weibull	NA	NA	NA	NA	NA
Gompertz	25192	4	25212	3	2
Log-logistic	25189	1	25209	2	=3
Lognormal	25224	5	25244	5	=3
Generalised Gamma	25191	3	25218	4	5
Second event					
Exponential	11267	5	11281	3	1
Weibull	NA	NA	NA	NA	NA
Gompertz	11260	3	11280	2	=2
Log-logistic	***11256***	***1***	***11276***	***1***	***=2***
Lognormal	11266	4	11286	5	=2
Generalised Gamma	11258	2	11285	4	5
Third plus event					
Exponential	4335	5	4348	5	1
Weibull	NA	NA	NA	NA	NA
Gompertz	4299	4	4319	4	=2
Log-logistic	***4292***	***2***	***4312***	***2***	***=2***
Lognormal	4299	3	4319	3	=2
Generalised Gamma	3494	1	3521	1	5

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion

Table 5. Comparison of extrapolation data for time to first event for a 30-year time horizon

	1 year		5 years		10 years		20 years		30 years	
	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC
[redacted] model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
REDUCE-IT KM curve (digitalised)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Extrapolation estimates from company model										
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care; KM – Kaplan-Meier

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Table 6. Comparison of extrapolation data for time to second event for a 30-year time horizon

	1 year		5 years		10 years		20 years		30 years	
	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC
[redacted] model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolation estimates from company model										
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care

Table 7. Comparison of extrapolation data for time to third plus event for a 30-year time horizon

	1 year		5 years		10 years		20 years		30 years	
	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC
[redacted] model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolation estimates from the company model										
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care

Table 8. Scenario analyses varying distribution for the first event in the secondary prevention population

Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential – Base case	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	9,723	0.385	0.490	19,848
Weibull	Placebo	14,009	11.192	7.863	-	-	-	-
	Icosapent ethyl	23,728	11.577	8.352	9,719	0.384	0.489	19,880
Gompertz	Placebo	13,813	11.239	7.908	-	-	-	-
	Icosapent ethyl	23,556	11.630	8.403	9,742	0.392	0.495	19,687
Log-logistic	Placebo	13,418	11.332	8.000	-	-	-	-

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Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
	Icosapent ethyl	23,386	11.687	8.456	9,968	0.354	0.456	21,838
Lognormal	Placebo	12,809	11.465	8.134	-	-	-	-
	Icosapent ethyl	22,974	11.800	8.569	10,164	0.335	0.435	23,379
Generalised Gamma	Placebo	13,658	11.271	7.941	-	-	-	-
	Icosapent ethyl	23,505	11.644	8.417	9,847	0.373	0.476	20,690

Abbreviations: ICER – Incremental cost effectiveness ratio; LYG – Life years gained; QALY – Quality adjusted life year

Table 9. Scenario analyses varying distribution for the second event in the secondary prevention population

Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	13,930	11.213	7.887	-	-	-	-
	Icosapent ethyl	23,685	11.609	8.387	9,755	0.397	0.500	19,499
Weibull	Placebo	13,950	11.161	7.828	-	-	-	-
	Icosapent ethyl	23,678	11.569	8.343	9,728	0.408	0.515	18,872
Gompertz	Placebo	13,956	11.102	7.756	-	-	-	-
	Icosapent ethyl	23,651	11.492	8.259	9,695	0.389	0.503	19,287
Log-logistic – Base case	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	9,723	0.385	0.490	19,848
Lognormal	Placebo	13,805	11.292	7.967	-	-	-	-
	Icosapent ethyl	23,711	11.632	8.408	9,907	0.340	0.441	22,440
Generalised Gamma	Placebo	13,958	11.184	7.854	-	-	-	-
	Icosapent ethyl	23,688	11.581	8.356	9,730	0.397	0.502	19,381

Abbreviations: ICER – Incremental cost effectiveness ratio; LYG – Life years gained; QALY – Quality adjusted life year

Table 10. Scenario analyses varying distribution for the third plus event in the secondary prevention population

Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	12,577	11.316	7.980	-	-	-	-
	Icosapent ethyl	22,833	11.664	8.437	10,255	0.348	0.457	22,451
Weibull	Placebo	14,230	11.183	7.853	-	-	-	-
	Icosapent ethyl	23,792	11.576	8.352	9,562	0.393	0.499	19,169

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Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Gompertz	Placebo	14,667	11.165	7.824	-	-	-	-
	Icosapent ethyl	24,381	11.541	8.307	9,714	0.376	0.483	20,115
Log-logistic – Base Case	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	9,723	0.385	0.490	19,848
Lognormal	Placebo	12,989	11.287	7.952	-	-	-	-
	Icosapent ethyl	23,282	11.627	8.400	10,293	0.340	0.447	23,009
Generalised Gamma	Placebo	NA	NA	NA				
	Icosapent ethyl	NA	NA	NA	NA	NA	NA	NA

Abbreviations: ICER – Incremental cost effectiveness ratio; LYG – Life years gained; QALY – Quality adjusted life year

Table 11. Comparison of all-cause mortality within the REDUCE-IT trial for secondary prevention and the proportion of death observed in the cost-effectiveness model

	REDUCE-IT (digitised)		Cost-effectiveness model	
			Base case	
Treatment	**Placebo**	**Icosapent Ethyl**	**Placebo**	**Icosapent Ethyl**
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]

Table 12. CV-specific ICD-10 codes

WHO codes	GHE cause name	ICD-10 codes
1100	Cardiovascular diseases	I00-I99
1110	Rheumatic heart disease	I01-I09
1120	Hypertensive heart disease	I11-I15
1130	Ischaemic heart disease	I20-I25
1140	Stroke	I60-I69
1150	Cardiomyopathy, myocarditis, endocarditis	I30-I33, I38, I40, I42
1160	Other circulatory diseases	I00, I26-I28, I34-I37, I44-I51, I70-I99

Abbreviations: GHE – Global health estimates; ICD – International Classification of Diseases; WHO – World Health Organisation

Table 13. UK CV-specific mortality rates

Age group	Male	Female
60 - 64	0.002583	0.001311
65 - 69	0.003724	0.001991
70 - 74	0.006509	0.00369
75 - 79	0.010641	0.006416
80 - 84	0.017957	0.01227
Over 85	0.041406	0.0336

Table 14. UK non-CV mortality rates

Age	Male	Female
60	0.0050413	0.0037562
61	0.0057653	0.0041962

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Age	Male	Female
62	0.0066833	0.0049732
63	0.0076473	0.0054262
64	0.0084243	0.0059802
65	0.0083732	0.0060292
66	0.0096952	0.0066182
67	0.0108182	0.0074332
68	0.0121402	0.0083922
69	0.0137162	0.0093692
70	0.011946	0.0088254
71	0.013975	0.0097374
72	0.016069	0.0116684
73	0.01932	0.0138094
74	0.022015	0.0156624
75	0.0212623	0.0152543
76	0.0251013	0.0180983
77	0.0289663	0.0212703
78	0.0338483	0.0250323
79	0.0386433	0.0286703
80	0.0375221	0.0269475
81	0.0439751	0.0323375
82	0.0508431	0.0379175
83	0.0603931	0.0456275
84	0.0705491	0.0537775
85	0.0579609	0.0415863
86	0.0714779	0.0530963
87	0.0846539	0.0644443
88	0.1014809	0.0788173
89	0.1205829	0.0928633
90	0.1319519	0.1104673
91	0.1552559	0.1294453
92	0.1770569	0.1487093
93	0.1995459	0.1694603
94	0.2288529	0.1941503
95	0.2587829	0.2240033
96	0.2932899	0.2531143
97	0.3172419	0.2746143
98	0.3479249	0.3073073
99	0.4118899	0.3326003
100	0.4344329	0.3809303

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The evidence and expert input available do not support the application of a treatment waning effect

Table 15. Scenario analyses assuming equal efficacy in the icosapent ethyl and placebo treatment groups following discontinuation in the secondary prevention population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case							
Placebo	13,970	11.201	7.871	-	-	-	-
Icosapent ethyl	23,693	11.587	8.361	9,723	0.385	0.490	19,848
Scenario – 20 years							
Placebo	13,970	11.201	7.871	-	-	-	-
Icosapent ethyl	23,685	11.577	8.355	9,715	0.376	0.483	20,098
Scenario – 10 years							
Placebo	13,970	11.201	7.871	-	-	-	-
Icosapent ethyl	23,862	11.526	8.309	9,892	0.325	0.438	22,609

Abbreviations: ICER – Incremental cost effectiveness ratio; LYG – Life years gained; QALY – Quality adjusted life year

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Full analysis for time to treatment discontinuation (TTD)

Table 16. Icosapent ethyl time to discontinuation goodness-of-fit statistics for the secondary prevention population

Distribution	AIC	Rank	BIC	Rank	Diff. Rank
Exponential	16045	7	16050.97	7	1
Weibull	***16007***	***1***	***16019***	***1***	***=2***
Gompertz	16026	5	16038	5	=2
Log-logistic	16011	4	16023	3	=2
Lognormal	16034	6	16046	6	=2
Generalised Gamma	16009	3	16027	4	7
Gamma	16007	2	16019	2	=2

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion

Table 17. Scenario analyses varying distribution for the time to treatment discontinuation in the secondary prevention population

Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	23,000	11.587	8.361	9,030	0.385	0.490	18,433
Weibull – Base case	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	23,693	11.587	8.361	9,723	0.385	0.490	19,848
Gompertz	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	24,511	11.587	8.361	10,541	0.385	0.490	21,517
Log-logistic	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	24,221	11.587	8.361	10,251	0.385	0.490	20,926
Lognormal	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	24,663	11.587	8.361	10,693	0.385	0.490	21,827
Generalised Gamma	Placebo	13,970	11.201	7.871	-	-	-	-
	Icosapent ethyl	23,214	11.587	8.361	9,244	0.385	0.490	18,870

Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years.

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Figure 26. Stratified Analysis of Time to the Primary Composite Endpoint from Date of Randomization with One Month Increment Timepoints ITT Population + Secondary Prevention

Abbreviations: HR – Hazard ratio; ITT – Intention to treat

Figure 27. Icosapent ethyl time to discontinuation observed KM curve vs. extrapolations for the secondary prevention population

Abbreviations: KM – Kaplan-Meier

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The company's model has been further validated with an external model developed for icosapent ethyl

Table 18. Clinical estimates from company model and cross-validation model in a secondary prevention population

	1 year		5 years		10 years		20 years		30 years	
	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC
First event: Total										
State-transition model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model - new preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
REDUCE-IT KM curve (digitised)	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Second event: Total										
State-transition model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model - new preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Third plus event: Total										
State-transition model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model - new preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuing icosapent ethyl										
State-transition model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model - new preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients alive										
State-transition model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model - new preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event free										
State-transition model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model - new preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – Best supportive care

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Table 19. **Comparison of validation model (state-transition) cost-effectiveness results to company model (PartSA)**

	Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
State-transition model	Secondary prevention	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model – new preferred base case – old list price		Icosapent ethyl	25,447	11.587	8.361	11,477	0.385	0.490	23,427
		BSC	13,970	11.201	7.871	-	-	-	-
PartSA model – new preferred base case – new list price		Icosapent ethyl	23,693	11.587	8.361	9,723	0.385	0.490	19,848
		BSC	13,970	11.201	7.871	-	-	-	-

Abbreviations: BSC – Best supportive care; ICER – Incremental cost effectiveness ratio; LYG – Life years gained; QALY – Quality adjusted life year

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Revised base case results

Table 20. Revised base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Placebo	13,970	11.201	7.871	-	-	-	-
Icosapent ethyl	23,693	11.587	8.361	9,723	0.385	0.490	19,848

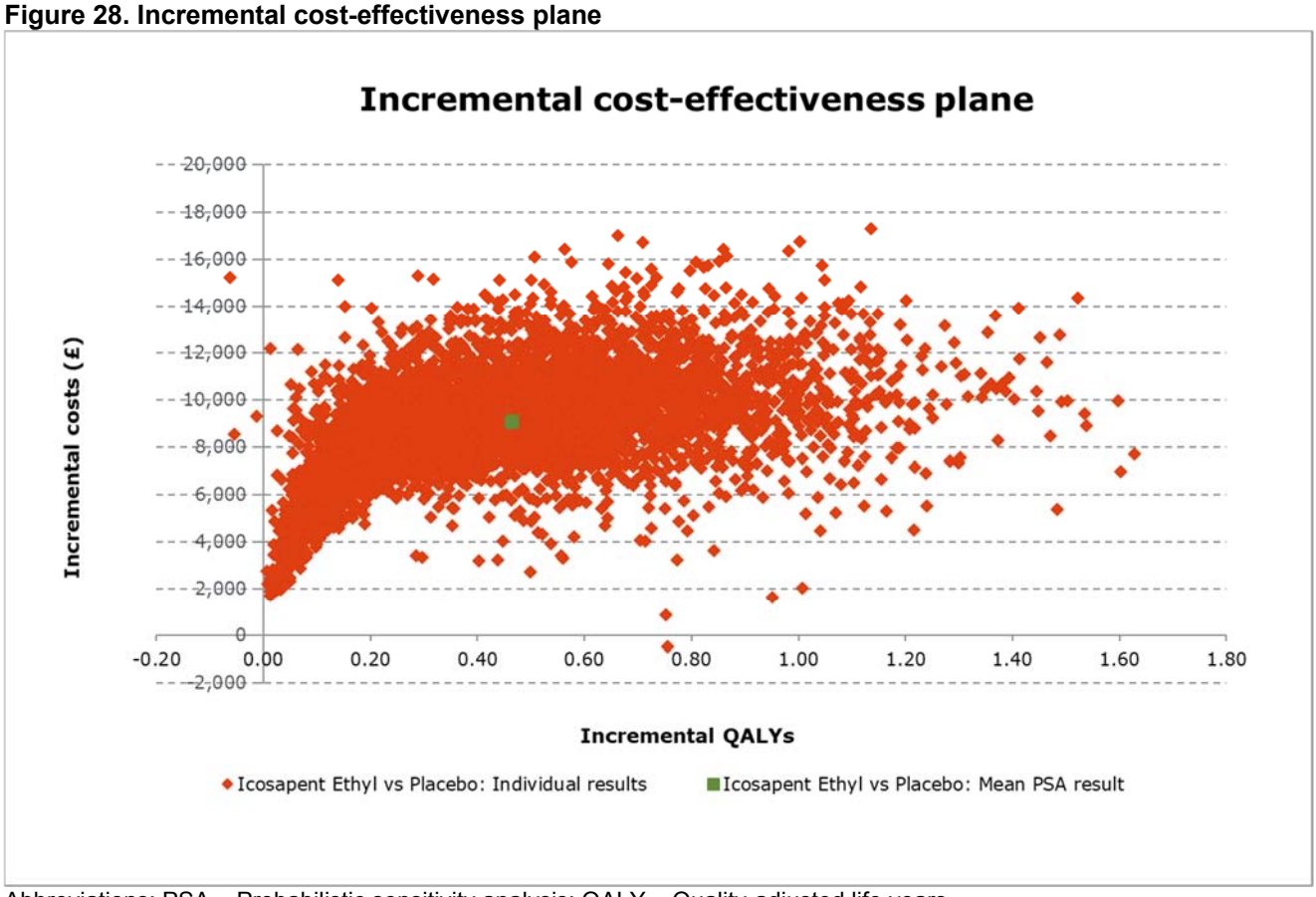
Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years.

Table 21. PSA results

Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£)
Placebo	14,373	7.636	-	-	-
Icosapent ethyl	23,470	8.099	9,097	0.464	19,625

Abbreviations: ICER – Incremental cost-effectiveness ratio; PSA – Probabilistic sensitivity analysis; QALYs – Quality-adjusted life years.

Figure 28. Incremental cost-effectiveness plane



Abbreviations: PSA – Probabilistic sensitivity analysis; QALY – Quality-adjusted life years

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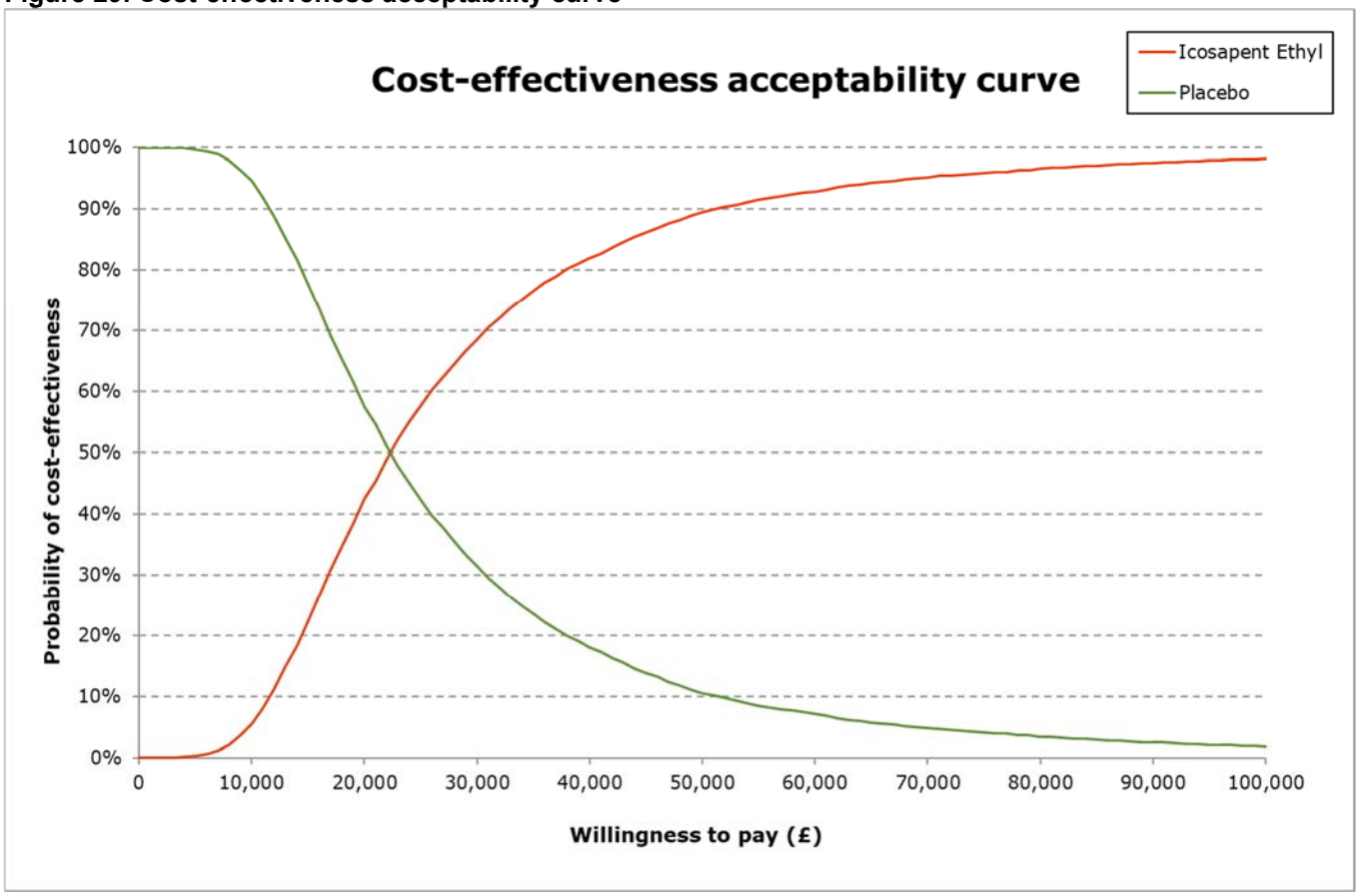
Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Tuesday 22 February 2022**. Please submit via NICE Docs.

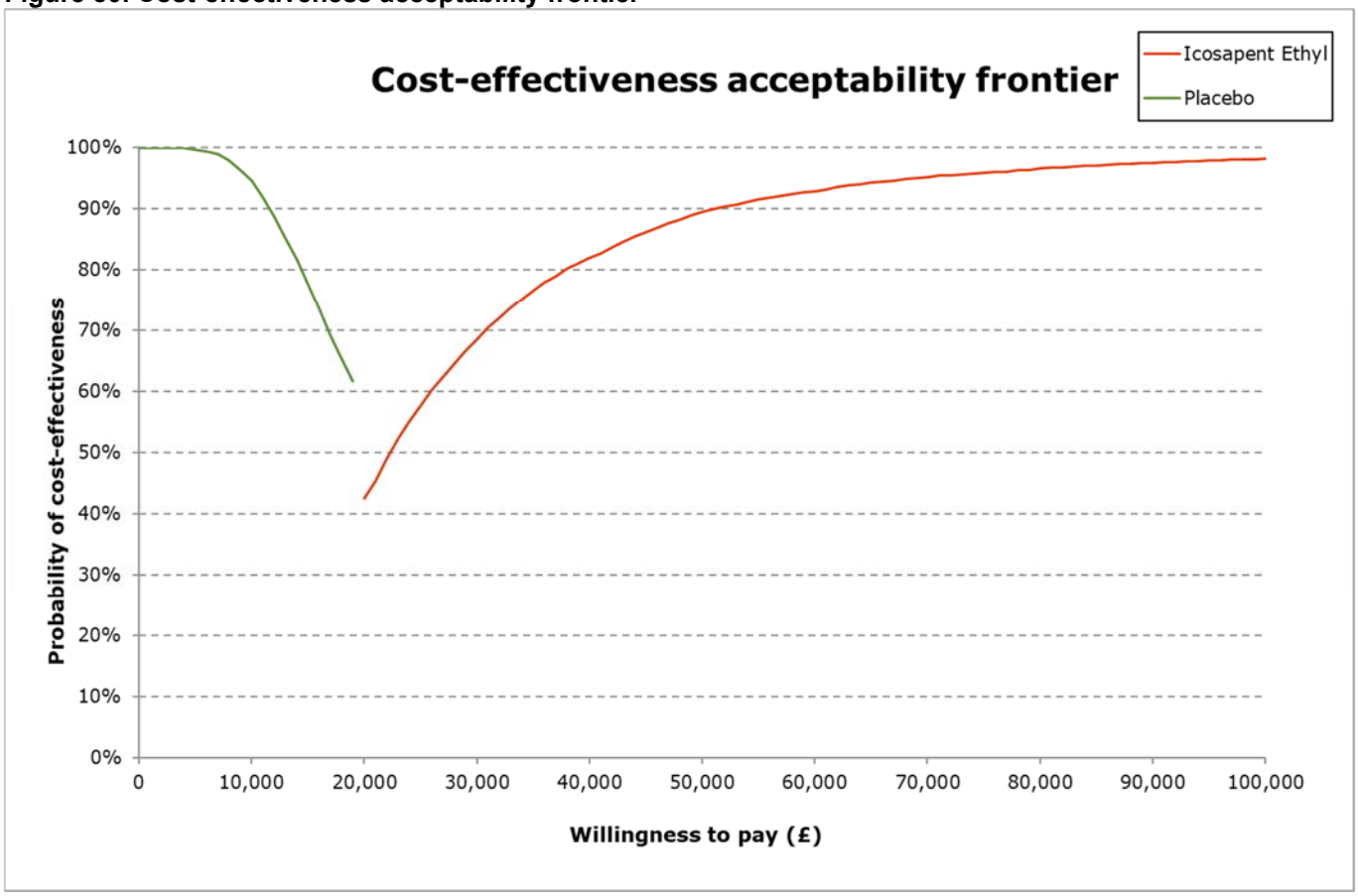
Figure 29. Cost-effectiveness acceptability curve



Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Tuesday 22 February 2022**. Please submit via NICE Docs.

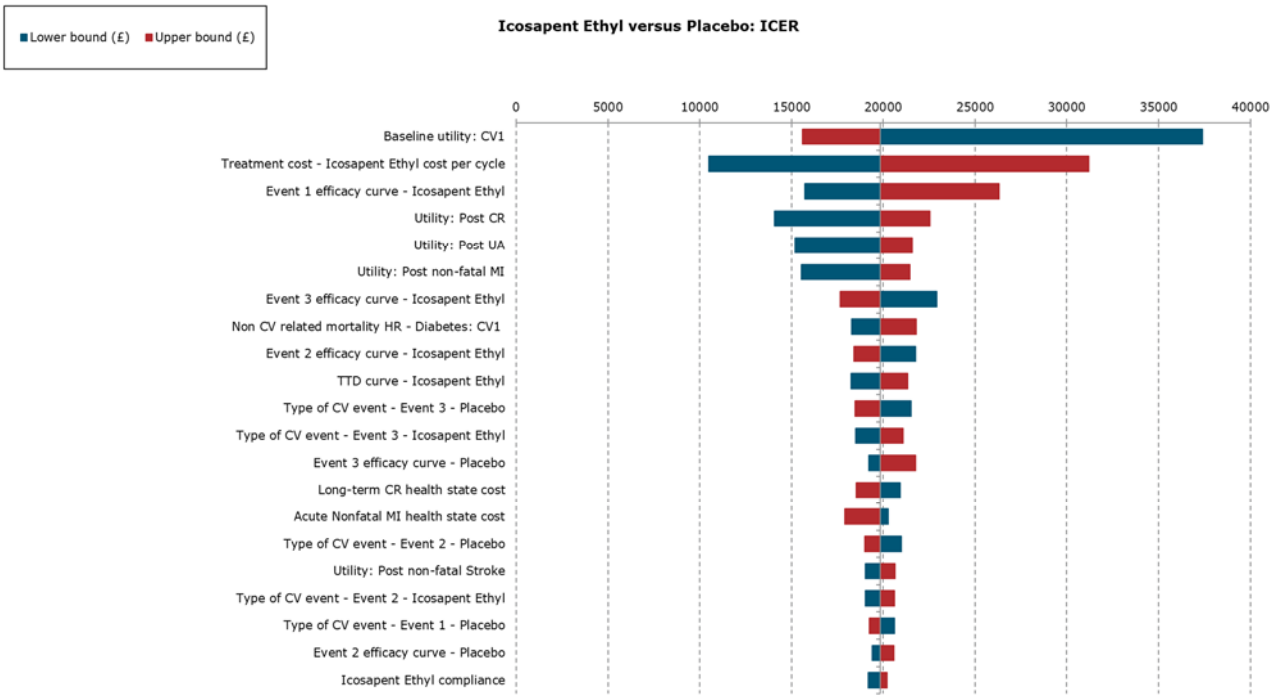
Figure 30. Cost-effectiveness acceptability frontier



Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Tuesday 22 February 2022**. Please submit via NICE Docs.

Figure 31. Tornado diagram for icosapent ethyl versus placebo



Abbreviations: ICER – Incremental cost-effectiveness ratio

Table 22. OWSA results for icosapent ethyl versus placebo

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Baseline utility: CV1	£37,405	£15,594	£21,811
Treatment cost - Icosapent Ethyl cost per cycle	£10,492	£31,208	£20,716
Event 1 efficacy curve - Icosapent Ethyl	£15,723	£26,316	£10,592
Utility: Post CR	£14,075	£22,556	£8,480
Utility: Post UA	£15,188	£21,592	£6,404
Utility: Post non-fatal MI	£15,522	£21,465	£5,943
Event 3 efficacy curve - Icosapent Ethyl	£22,926	£17,647	£5,279
Non CV related mortality HR - Diabetes: CV1	£18,275	£21,781	£3,506
Event 2 efficacy curve - Icosapent Ethyl	£21,751	£18,395	£3,356
TTD curve - Icosapent Ethyl	£18,245	£21,344	£3,099
Type of CV event - Event 3 - Placebo	£21,503	£18,473	£3,030
Type of CV event - Event 3 - Icosapent Ethyl	£18,481	£21,079	£2,598
Event 3 efficacy curve - Placebo	£19,211	£21,767	£2,556
Long-term CR health state cost	£20,935	£18,528	£2,407
Acute Nonfatal MI health state cost	£20,273	£17,915	£2,358
Type of CV event - Event 2 - Placebo	£20,985	£18,992	£1,993
Utility: Post non-fatal Stroke	£19,035	£20,655	£1,619
Type of CV event - Event 2 - Icosapent Ethyl	£19,038	£20,627	£1,589

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Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Type of CV event - Event 1 - Placebo	£20,620	£19,245	£1,375
Event 2 efficacy curve - Placebo	£19,391	£20,588	£1,198
Icosapent Ethyl compliance	£19,190	£20,217	£1,028

Abbreviations: CR – Coronary revascularisation; CV – Cardiovascular; ICER – Incremental cost-effectiveness ratio; MI – Myocardial infarction; OWSA – One-way sensitivity analysis; UA –Unstable angina

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Tuesday 22 February 2022**. Please submit via NICE Docs.

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Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Tuesday 22 February 2022**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	HEART UK – The Cholesterol Charity
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Tuesday 22 February 2022**. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	There is a clear unmet need. IPE may be of benefit to high risk patients who are on maximal tolerated statin and ezetimibe and who have persistently elevated fasting triglycerides (1.5-5.6 mmol/L) despite maximal tolerated statin and ezetimibe but well controlled LDL-C, below the Inclisiran threshold. IPE offers something for many patients in this category who are not eligible for other novel therapies recently recommended by NICE.
2	As an omega 3 product, patient acceptability is likely to be high.
3	There has been discussion about the Reduce-IT trial that the placebo (mineral oil) might be harmful rather than neutral, but in our opinion that effect is not big enough to explain away the effectiveness of the drug.
4	Fishy burbs do not appear to be a problem for the majority of people. This uncommon side effect is not as bad as having a heart attack or stroke!
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your

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Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Tuesday 22 February 2022**. Please submit via NICE Docs.

comments on the appraisal consultation document, please submit these separately.
Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

In my opinion, and for the reasons provided in my commentary below, the interpretation of the evidence regarding the issue of mineral oil is not reasonable, because the totality of the evidence unambiguously favours of the assessed intervention. Moreover, citing this highly debatable issue as one the potential reasons for not recommending this product in the UK, against the overwhelming evidence of both the magnitude of cardiovascular benefit, as well as the quality of the evidence (contemporary, large randomised double-blind clinical trial), is clearly not reasonable.

- Recommendations – section 1

The reported uncertainty about "how well icosapent ethyl (IPE) works because it was compared with a placebo that may itself increase cardiovascular risk" is entirely hypothetical and, as such, should not be the driver of a negative recommendation for a product that has unambiguously substantiated a clinically relevant cardiovascular effect in a large, contemporary, double blind cardiovascular outcomes trial, and which could reduce significantly cardiovascular outcomes, including death, in the UK.

The issue of putative effects of mineral oil has extensively studied by regulators, which have concluded that even under very conservative assumptions about potential negative effects due to comparators, the Vazkepa was associated with a risk reduction of at least 16.5%. (Vazkepa European Public Assessment Report). The US FDA has reached the same conclusion.

Moreover, the putative effects of mineral oil on absorption of concomitant drugs and biomarker levels does not have impact on the efficacy on cardiovascular events of IPE, because, as shown in the Reduce-it study, the cardiovascular benefit observed with IPE is undistinguishable between subgroups of higher/lower TG, LDL, hsCRP, and virtually every other subgroup (N Engl J Med 2019; 380:11-22).

To finalize, the placebo rates of CV events in other contemporary trials in patients with established cardiovascular disease are very similar to those observed in the Reduce-it study, such us in Fourier study, approximately 15% rate at 3 years (N Engl J Med. 2017;376(18):1713-1722), or Improve-it, with approximately 25% rate at 5 years (N Engl J Med. 2015;372(25):2387-2397). A significant deleterious effect of mineral oil placebo on CV events would have translated in significantly higher

rates compared to other studies. That has not been the case.

In essence, the hypothesis of the deleterious effect of mineral oil cannot and does not explain the profound clinical benefit observed with IPE, actually in both primary prevention (albeit with more uncertainty) and secondary prevention populations.
As it relates to the generalizability of the evidence to the Uk population, the report notes two issues: people with South Asian family backgrounds may benefit more from icosapent ethyl (this issue, therefore, could only result in greater benefit for IPE) and the fact that other recommended treatments were used by only a small proportion of people in Reduce-it, notably inclisiran or SGLT2 inhibitors.
As it relates to inclisiran, its benefit on cardiovascular outcomes has not been proven and the population in the Reduce-it study had relatively well controlled LDL levels within range.
As it relates to SGLT2 inhibitors, these are indicated only in diabetic individuals, and note to other non-diabetic individuals with remaining cardiovascular risk.

Name	Multiple signatories
Role	Not specified
Other role	Not specified
Organisation	EPADI (The EPA Drug Initiative)
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

EPA Drug Initiative (EPADI) [1]

February 17, 2022

FOR THE ATTENTION OF:

National Institute for Health and Care Excellence,
Technical Appraisal Team
2 Redman Place, London E20, United Kingdom
TATeam4@nice.org.uk
nice@nice.org.uk

Re: Comments Regarding Appraisal Consultation Document ID3831
Icosapent Ethyl with Statin Therapy for Reducing the Risk of Cardiovascular Events in People with Raised Triglycerides

Hello,
We are the signatories representing EPADI (The EPA Drug Initiative). EPADI is an international group of Physicians, patients, and concerned citizens (since 2012), who are bound by a common conviction: that highly purified EPA, as found only in VASCEPA/VAZKEPA, has been shown to offer significant value in the prevention and treatment of cardiovascular disease. This cover letter and document is the EPADI's response to the **N.I.C.E. "Call for Comments" on their Consultation Document ID 3831**, "*Icosapent Ethyl with Statin Therapy for Reducing the Risk of Cardiovascular Events in People with Raised Triglycerides.*"

In reply to the call for feedback regarding N.I.C.E. Appraisal Document ID3831, we are **profoundly troubled** that the committee has formally concluded in **Section 3.8** that ***"the treatment effect of icosapent ethyl is uncertain because of the mineral oil placebo in REDUCE-IT" and that "mineral oil was not a true neutral oil and may have increased the risk of a cardiovascular event in the placebo group."***

This view belies a wealth of emerging evidence to the contrary for the treatment of cardiovascular- related disease that is now well-established in public forums, professional meetings, publications, and other national/international appraisal committee meetings.

[1] EPADI Please reference (http://epadruginitiative.com/) for more details.

We do not believe that the Committee has considered all the relevant data regarding this assessment and the implications on matters of national health are enormous. [2] Furthermore, we believe the committee has missed the mark in the Appraisal Document and, in our view, is providing misleading and distorted information based upon an incomplete review of the relevant evidence.

Therefore, it is our **strong recommendation that the mineral oil findings of the committee be discounted entirely** in accordance with the evidence and discussion that we present in the **Appendix** to this cover.

Best Regards,
Select EPADI Supporters of this Response Document

[2] According to the Journal of the American College of Cardiology ischemic disease and strokes "are the leading cause of global mortality and a major contributor to disability". Furthermore, the European Society of Cardiology has branded cardiac disease as being "the biggest epidemic in human history." In the United Kingdom alone the Global Burden of Disease database (2019) estimated combined deaths from IHD and Ischemic Stroke to top 127,000 with a prevalence of 2.6 million. In the age of COVID This trend is increasing.

Appendix

This Appendix includes two parts. In the first, we highlight the well-established and recognized findings and conclusions of several expert bodies that show that the committee 'got it wrong' and draw upon other evidence of need and changing perspectives. To make the document as concise as possible, finding titles are 'hot-linked' to the underlying report. The second part includes contact and background information for the signatories and their testimonials.

Part 1 - Previous Studies and Analyses

The mineral oil placebo issue has received attention in the past and intense scrutiny since the release of the REDUCE-IT Trial results. None has found a matter of concern with its use as a placebo. An outline of the studies and their findings is presented below.

1. **EMA-CHMP Conclusion**

   The EMA's VAZKEPA-epar Public Assessment Report writes that "**in a worst-case scenario attributing all of these effects to mineral oil, a putative negative impact of mineral oil on MACE should not account for more than 0.3-3.0% of MACE events**. (EMA/145271/2021, p. 122)

2. **The U.S. FDA Endocrinologic and Metabolic Drugs Advisory Committee**

   Key excerpts from this review include:

- **"No strong evidence for biological activity of the mineral oil placebo was found by the REDUCE-IT cardiovascular outcomes trial."** Furthermore, this analysis is consistent with two prior FDA reviews of mineral oil in the MARINE and ANCHOR trials (both using icosapent ethyl with a mineral oil placebo).

- In the REDUCE-IT trial the FDA directed an **independent Data Monitoring Committee, or DMC** to examine un-blinded data on an ongoing basis over a period of several years and to specifically look for a signal of biological activity from the mineral oil placebo." As previously stated, "**No strong evidence for biological activity of the mineral oil placebo was found."**

- **Literature reviews support the conclusion that light mineral oil does not exert clinically meaningful effects on medication (including statin) or nutrient absorption or efficacy, changes in lipids or other biomarkers, or changes in patient safety.**

- Because of the established history of mineral oil use, and because it was the best-suited placebo for studies of icosapent ethyl, the FDA agreed the development and regulatory program for icosapent ethyl **did not require any additional mineral oil-specific testing.**

3. **The EVAPORATE Trial (NCT02926027): Effect of VASCEPA on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy**

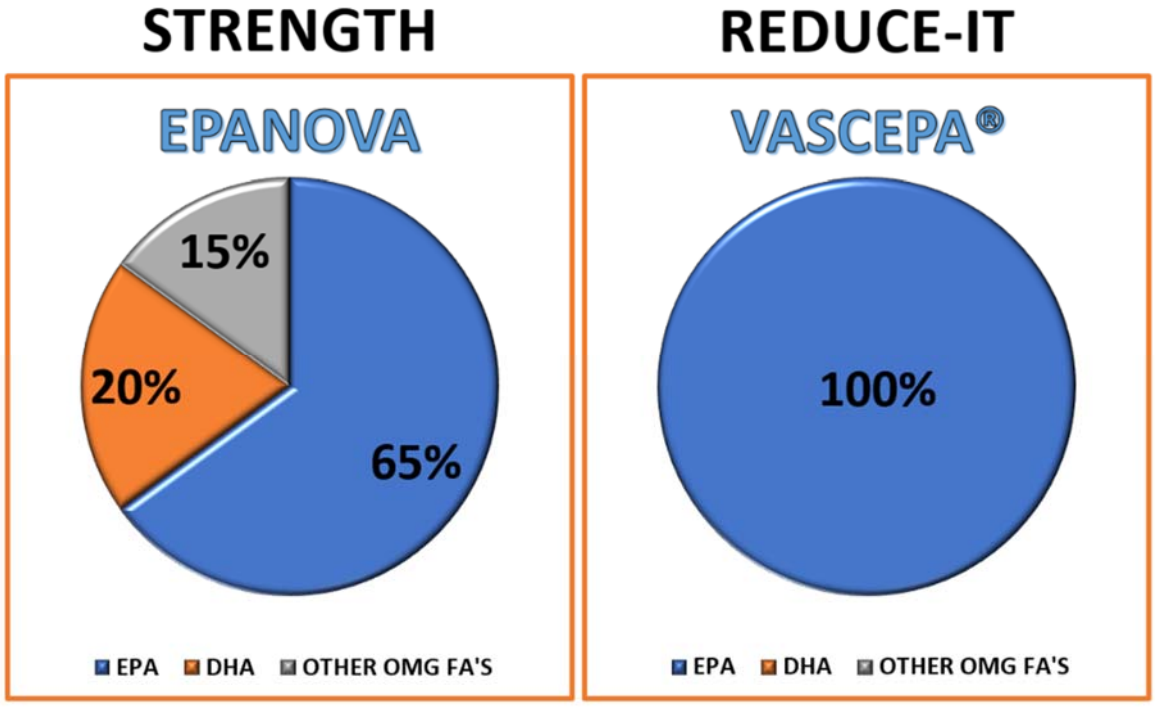
The EVAPORATE Trial was an imaging study to evaluate whether the treatment with VASCEPA (4 grams/d) results in a greater change from baseline in low attenuation plaque than placebo in subjects with elevated triglycerides (200-499 mg/dl). The subjects in the mineral oil placebo arm were compared to patients in a second study (GARLIC5), that used a **cellulose-based placebo** to evaluate plaque progression. The two comparators showed nearly identical plaque progression.

4. **JELIS (Japan EPA Lipid Intervention Study**

The Primary Outcome Measures in this 2005 trial were MACE (as in REDUCE-IT). The intervention Arm consisted of a high-purity EPA preparation dosed at 1.8 g/d in a Japanese population, for whom the baseline EPA levels are higher than in western populations due to greater dietary intake of marine omega-3 fatty acids. There was **NO placebo** arm in this study. JELIS produced **a 19% RRR in the 5-point MACE.**

5. **The STRENGTH Trial: (NCT02104817)**

Your appraisal document mentioned the failed results of the STRENGTH Trial and erroneously compared the active arm in STRENGTH to the active arm in REDUCE-IT as being "Similar." to each other. This analogy is wrong. The two drugs used in the studies are completely dissimilar.
EPANOVA, the drug used in STRENGTH is a carbolic acid mixture of EPA (65%) and DHA (20%) and other compounds (15%), whereas the REDUCE-IT Trial used icosapent ethyl (VASCEPA®) which is at least 97% pure EPA with no other Omega-3 FA's or derivatives included in the mixture, as depicted below.



The mixture is an important distinction that we feel has been lost on your committee. These are totally different drugs. The Committee statement referenced above seems to imply that the only meaningful distinction in the two active arms was the placebos.
Brian Olshansky et al. concluded in their EHJ paper "*Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies"*:
The preponderance of evidence identified in this review confirms that **mineral oil is essentially inert**, with no systemic effects in humans when taken orally, other than a lubricating laxative effect in the gastrointestinal tract. While some changes in select biomarkers were reported in REDUCE-IT patients randomized to mineral oil placebo, similar increases in lipid biomarkers within statin-treated patients have been seen in other contemporary lipid CV outcome trials, and importantly, **no clinical impact of such biomarker changes in the REDUCE-IT placebo group was observed.** Prespecified and *post hoc* analyses of REDUCE-IT support that on-treatment EPA levels, **not the choice of placebo overwhelmingly** accounted for the robust REDUCE-IT clinical findings. **Multiple analyses by distinct and independent groups conclude that even if theoretical mineral oil effects were real, such effects would be small and would not impact study conclusions or the robustness of the CV event risk reduction observed in REDUCE-IT.**

Furthermore, "If mineral oil placebo affected statin absorption, then LDL levels would predict outcomes, but TG and LDL levels in the placebo arm of REDUCE-IT did not predict MACE or any other outcome."

The Primary Investigator in the STRENGTH trial whose public comments regarding mineral oil and the success of REDUCE-IT and the demise of STRENGTH were the result of the placebo's used in each trial respectively. These are theoretical assertions and do not reflect the scientific conclusions behind dozens of meta-studies and Randomized Placebo-Controlled Clinical Trials (RCT's). Such comments completely jump the tracks of the Scientific Method and divert the attention away from the real metric in these failed trials, as depicted in the following Table. The real cause for failure may be the presence of and the interaction of DHA. **Not the placebo**.

STUDY	PATIENT POPULATION	FORMULATION & DOSE	PLACEBO	OUTCOME
JELIS (2007)	N= 18,645 on statins	EPA 1800 mg/d	NONE	
ORIGIN (2012	n= 12,536, high risk cv events	EPA + DHA 840 mg/d	Olive Oil	
ASCEND (2018)	n= 15,480, w/diabetes	EPA + DHA 840 mg/d	Olive Oil	
VITAL (2019)	n= 25,871, m/w age >50	EPA + DHA 840 mg/d	Olive Oil	
REDUCE-IT (2019)	n= 8,179, cvd on statins	EPA 2X2 g/d	Mineral Oil	
STRENGTH (2020)	n= 13,086, cvd on statins	EPA+DHA 2X2 g/d	Corn Oil	

6. Additional Studies Involving Mineral Oil as a Placebo

The analysis completed by the European Heart Journal screened 281 studies, of which 80 used mineral oil as a placebo.

This comprehensive review found no consistent pattern of changes in lipid levels and inflammatory markers in patients given mineral oil. Even in those studies where statistically significant changes were reported, changes were generally small and were of no clinical significance. No relevant safety concerns, including CV AEs, have been identified with oral administration of mineral oil, including in children receiving a high volume to treat constipation.

7. The European Atherosclerosis Society – Findings Statement 3.5

In reviewing the success of the REDUCE-IT trial and the failure of the STRENGHT Trial, the Task Force concluded:

- The discrepant results of the REDUCE-IT and STRENGTH trials raise many questions. Both studies enrolled statin-treated patients at high cardiovascular risk with elevated TG levels at baseline (median 2.4 mmol/L [212 mg/dL] in REDUCE-IT and 2.7 mmol/L [240 mg/dL] in STRENGTH); patients in STRENGTH also had low HDL-C (median 0.93 mmol/L [36 mg/dL])]. REDUCE-IT showed a significant 25% reduction in major adverse cardiovascular events with high dose icosapent ethyl compared with a mineral oil comparator after treatment for a median of 4.9 years.
- **This clinical benefit was higher than that predicted by the magnitude of TG-lowering (18%), implying that non-lipid pleiotropic mechanisms of EPA must be implicated**. Furthermore, the EVAPORATE trial, which also compared high-dose icosapent ethyl with the same mineral oil comparator, showed slowing of plaque progression and reduction in plaque volume over 18 months.

- In contrast, the **STRENGTH trial comparing high-dose EPA/DHA with corn oil, was stopped prematurely for futility after 42 months, despite 18% TG reduction as in REDUCE-IT**.

8. Other Comments

Further context regarding the scope and burden of heart disease and changing perspectives towards acceptance of icosapent ethyl may be helpful.

The Current Burden That Could Be Avoided or Mitigated

According to the Global Health Data Exchange (Global Health Data Exchange | GHDx) ischemic heart disease (IHD) and ischemic stroke (IS) remain the #1 and #2 leading causes of death in the UK and worldwide. In the UK (2019), the prevalence for IHD (all ages), approached nearly 2 million while IS topped half a million. IHD deaths in adults 55+ hit 90,000, while IS deaths topped 33,000. The DALY's in all age groups

are well over 1.25 million! These are the numbers expected to be reduced by treatment with VASCEPA® within the National Health System of the UK.

The economic and health burdens of cardiovascular disease in the UK are enormous. Ischemic Heart Disease remains a major threat to public health, and the overall burden is increasing globally. In some locations over the past 5 years, including parts of the **United Kingdom**, age-standardized IHD death rates are increasing, ***suggesting that long-term declines in IHD due to improved prevention and health care are no longer occurring in these locations***. The cost of CVD burden stands at €210bn a year in the European Union (EU) alone, with both the health and economic burden of CVD set to grow exponentially in Europe and across the globe in the coming years.

We urge **NHS England to focus on delivering effective interventions that will reverse these trends, including those that prevent and control cardiovascular disease**. It's no wonder that the European Society of Cardiology has branded cardiovascular disease to **"be the biggest epidemic in human history"**

Changing Perspectives and Guidelines

The current management of cardiovascular disease, with a primary focus on LDL-C, does not optimize risk prevention for large numbers of patients. Therefore, there is a need to look beyond LDL-C and consider the importance of other risk markers, like serum triglycerides, in all at-risk patients. In association with an increasing prevalence of obesity and Type 2 diabetes in recent decades, the number of patients with elevated triglycerides has increased and will continue to rise in parallel.

Guidelines are now starting to acknowledge the growing evidence and role of triglycerides in cardiovascular disease management: The 2019 European Society of Cardiology/European Atherosclerosis Society guidelines recommend the measurement of triglycerides as part of the routine full lipid analysis approach. As CVD management broadens, focusing beyond LDL-C treatment will become an increasingly important measure in the ambitious goal of reducing the vast global burden of this disease.

We believe that the Randomized Clinical Trials (RCT) like MARINE, ANCHOR, REDUCE-IT, CHERRY, EVAPORATE and even STRENGTH demonstrate the pleiotropic effects of icosapent ethyl that go beyond lipid management to REDUCE the risk of a MACE in high-risk patients**. These effects are significant and abundant in both a Primary and a Secondary setting.** These beliefs are also reflected in the Treatment Guidelines recommended by 20+ Medical Societies including.

- **European Society of Cardiology**
- **European Atherosclerosis Society**
- **European Association of Preventive Cardiology**
- ***New 1/10/2022 AHA Scientific Statement Cardiovascular Risk Reduction in adults with type2 diabetes**

The American Heart Association along with the American Diabetes Association are recommending the use of icosapent ethyl in a **Primary Prevention setting**:

The AHA Scientific Statement:
"Icosapent ethyl at a dose of 4/d, as well, should be considered given ***the 30%*** *additional cardiovascular risk reduction in the REDUCE-IT trial."*

Finally: The World Health Organization says, *"the key to cardiovascular disease reduction lies in the inclusion of cardiovascular disease management interventions in universal health coverage packages."* We, therefore, encourage this Committee to reconsider their previous findings and for the health benefit of all UK citizens recommend the inclusion of icosapent ethyl in a broad primary and secondary setting.

Part 2 - Signatories/Testimonials

We, the undersigned, submit our names and testimonials of the health benefits associated with the use of icosapent ethyl in primary and secondary prevention and treatment of cardiovascular disease. Furthermore, we see these benefits extending into treatment and possible intervention for other indications. Therefore, we are in support of EPADI's Comments Regarding Appraisal Consultation Document ID3831 "Icosapent Ethyl with Statin Therapy for Reducing the Risk of Cardiovascular Events in People with Raised Triglycerides."

[redacted]
Company Director
UK resident
MSC - Aston University, Birmingham
Reason for support: NHS heart patient, lost family members to heart disease including mother and two cousins who died at 59 and 63 and for whom Vascepa may have extended their lives.
[redacted]

[redacted]
Graphic Designer
UK resident
Reason: Following the progress of Vascepa for the past 11 years, I firmly believe in the science, trust it is safe. As a UK citizen who trusts the NHS to ensure the best medicines are available, I am shocked that there would be any doubt about Vascepa. As I am getting older, I would like Vascepa to be available if I need it to control my triglycerides and/or cholesterol. Both of my parents died too young from heart conditions that would have been treatable with Vascepa had it been available. The real risk is in not having it available in the UK!
[redacted]

[redacted]
UK Resident
Company Director
BA Hon[a] Education Manchester University
Reason for support: My father passed away after a massive heart attack aged 44. Also I take over the counter EPA which I am not sure what is in it. Vascepa has completed a 5 years very successful outcome study, with outstanding results and I feel UK residents are missing out if the NHS is denied Vasepa.
[redacted]

[redacted]
Texas Professional Geoscientist
[redacted]
USA Citizen
B.S. Geology, Brigham Young University
I've been a patient on VASCEPA® for over 7 years. My doctor started me on a statin in early 2014 because my TC exceeded 250 mg/dl. After 6 months on pitavastatin my lipid panel was still high: TC 210, TG 156, HDL 54, LDL 125. Nine months later I added VASCEPA® to the statin therapy. At my 3-month checkup after that my lipid panel showed a 32% improvement in TC and a whopping 43% reduction in both LDL and TG: TC 152 (-32%), TG 101 (-43%), HDL 51 (-6%), LDL 81 (-43%). VASCEPA® is a "Supercharger" to statin therapy! As a side benefit, I used to suffer with gout flare ups (2-3 times/year). I haven't had a single flare up since being on VASCEPA.

[redacted]

[redacted]

Technology Consultant
USA
MBA / BS Computer Science - Rutgers University
Family history of heart disease. Grandfather and Great Uncle died from heart disease. Uncle recently had a heart attack. Father has a stent and has been under treatment for CVD for numerous years. Providing patients with all available treatment options and knowledge is paramount, without muddying the waters with disproven theories regarding mineral oil placebos. The goal of health agencies worldwide should be to improve the lives and health of those people they represent.
[redacted]

[redacted]

USA
Associate degree Raritan Valley Community College
Family history of heart disease. My older brother recently had a serious cardiovascular event. Providing patients with all available treatment options and knowledge is paramount, without muddying the waters with disproven theories regarding mineral oil placebos.
[redacted]

[redacted]

USA
MBA Auburn University
Family history of heart disease. Father and uncle died of heart disease. I have a stent and have been under treatment for risk factors for over a decade. Providing patients with all available treatment options and knowledge is paramount, without muddying the waters with disproven theories regarding mineral oil placebos.
[redacted]

[redacted]

US Department of Homeland Security - Retired
Citizen/Resident of the United States
Bachelor's Degree - State University of New York @ Fredonia
I have been taking Vascepa for over 8 years due in large part to my family's history of heart disease. I have lost multiple family members due to CVD - to include a brother who died at the age of 54.
[redacted]

[redacted]

Retired Pharmaceutical Chemist
Citizen/Resident of the United States
B.Sc. Chemistry - Carleton University
I have been taking Vascepa for over 3 years. Mother died of heart disease and younger brother had triple bypass.
[redacted]

[redacted]

Pastoral Associate, Retired
BA Michigan State University, MPA Assumption University
USA
Family history of heart disease. Prescribed Vascepa (4gms/day) in 2017 - present wherein all cardiovascular risk markers have shown significant improvement.
[redacted]

[redacted]
Electrical Engineering Professor
Citizen/Resident of the United States
B.S. Physics - Miami (Ohio), M.S. & Ph.D. Electrical Engineering - U. Illinois Urbana-Champaign
Family history of heart disease. Father died of congestive heart failure, great grandfather of heart attack. Have concerns over (and under physician care for monitoring) personal elevated cardiovascular risk due to moderately high cholesterol.
[redacted]

[redacted]
Pharmacist
Canada
Cardiovascular disease Pt and Pt advocate.
I see Pts daily who are at high risk of a heart attack, stroke, or revascularization who meet the REDUCE-IT criteria who could have their chance of survival significantly improved with the use of Vascepa. During the trial, for every 6 Pts on Vascepa 1 Major Adverse Cardiac Event was prevented (and all the emotional, financial, and societal repercussions that go with that event).
[redacted]

[redacted]
General Manager
USA
BS Business Management - University of Dayton
CVD is the number one cause of death across the globe. The cost burden of CVD on society has been tremendous and is trending in the wrong direction. Governments and regulators often talk about the need for safe, effective, and affordable treatment options. Vazkepa is the biggest advancement for treating CVD in the last three decades. The results of the REDUCE-IT trial clearly show that Vazkepa is safe and effective. The Institute for Clinical and Economic Review found that icosapent ethyl represents a high long-term value for the treatment of CVD.
[redacted]

[redacted]
MBA - Supply Chain Management
Czech Republic
Reason: Supporting rapid acceptance and proliferation of innovative CVD medications like VASCEPA/Icosapent Ethyl throughout EU and UK will help VAZKEPA succeed in smaller EU countries, like Czech Republic, where my mother died due to limited availability of newest breakthrough medications, especially in CVD field.
[redacted]

[redacted]
Registered Nurse, BSN

Citizen/Resident Minnesota, USA
27 years working experience in Cardiovascular Intensive Care. Untold numbers of patients cared for suffering from CHD, CHF, Cardiomyopathies, Valvular Dz, PAD, PVD, CVA, Renal Dz, and Hepatic Dz all with highly impacted lives of pain, suffering, and monetary loss that Reduce- It has shown could be reduced or eliminated by widespread use of Vascepa/Vazkepa. With the widespread overburdening of our health care systems worldwide, it seems malpractice to not be providing the best medications available which will ultimately positively affect humanity as well as decrease the burden on individuals and the health care system.
[redacted]

[redacted]
Europe, Denmark
IT Engineer, Retired
Private companies in farming, plant breeding for food production.
Have seen several members of me, and wife's family die of CDV problems, heart attack, stroke. Several of the men still alive have had serious heart surgery, typical bypass operation and are on permanent statins. Vazkepa will - without question - help these CVD patients live longer and have a better life.
[redacted]

[redacted]
IT engineer, Computer HW Architect
USA
My mother-in-law died of CDV problems, heart attack last year. Due to COVID, my husband even had no chance to go back for this. With VASCEPA for two years, my heart health has improved without issues now. My mother-in-law was in China. Unfortunately, she cannot wait for this magic medicine to be available. I really wish this medicine can be available to all the people and all the countries to save people. Believing in science is the nature of my blood. If you look at all the testing results, it is really a medicine that every country should encourage people to take. I do believe it potentially cures other serious illnesses and improves people's health.
[redacted]

[redacted]
Attorney / Partner
West Virginia, USA
I am currently taking Vascepa and believe it has provided clinic benefits. I take Vascepa for added protection from another CV event.
[redacted]

[redacted]
USA
Engineer
I believe in the science and know multiple people already benefiting from Vascepa.
[redacted]

[redacted]
Retired Nissan and Ford automotive dealer.
Citizen/Resident of the United States

BS Business Management - University of New Orleans
I have been taking Vascepa for 4 years. I have controlled high cholesterol and controlled high blood pressure. I also had Myocarditis because of coronavirus which caused noticeable heart damage with a reduction in my ejection fraction. After taking Vascepa my blood work is now perfect, my ejection fraction has returned to normal levels, and I feel great. I have lots of energy, even noticed a difference in my skin and hair.
[redacted]

[redacted]
Retired Mechanical Engineer
Citizen of USA
I was prescribed Vascepa February 2019 due to hypertension and family history of heart disease, my father died of his third heart attack at age 67. My brother, who is 12 years younger than me, received six stents at age 57 for 90% blockages. He is prescribed Vascepa for treatment of atherosclerosis. My mother suffered a permanently disabling stroke at age 69 and spent 15 years in a nursing home. My sister who is 3 years younger than me was admitted to a nursing home at age 61 for early onset Alzheimer's Disease. A trial (BRAVE-EPA) is under way to explore treatment of Alzheimer's Disease with Vascepa. I have experienced no adverse side effects from long term use of Vascepa.
[redacted]

[redacted]
USA
Pure EPA or Vascepa was proven in the JELIS trial and later confirmed in the Reduce It trial to lower cardiovascular death, MI and stroke in the range of 20 to 30% relative risk reduction in addition or beyond the established benefit of statins alone. This was accomplished with very few if any side effects nor any drug interactions. This lifesaving medication has been found to be very cost effective by independent reputable researchers. Please research this for the sake of others. I would add that in the studies it did not matter what level of triglycerides were present, the benefit was near the same at all levels tested.
[redacted]

[redacted]
Retired Chemist & Computer Specialist
Citizen of USA
MS Microbiology & Biochemistry
Have been on VASCEPA for over 2 years now.
Clinical trials have proved its value for heart patients!
[redacted]

[redacted]
LEAN Specialist-Engineer
USA Citizen
I am a 59-year-old user of this medication. I have not had any CVD events. My doctor prescribes Vascepa and statin as a CVD preventative based on my cholesterol levels and family

history. Have taken Vascepa for 3 years. What I noticed a month after starting the medicine is the tightness in my chest subsided. My blood pressure is a little lower, 180/20 when I donated blood a few weeks ago. Trigs are reduced. 180 before Vascepa, 140 when last checked a year ago.

[redacted]

[redacted]
Doctorate in Veterinary Medicine-Veterinarian
USA Citizen
I started my journey with Omega 3 Fatty Acids about 12 years ago. At that time, I saw that Amarin was performing a study on a highly purified form of EPA called Icosapent Ethyl for lowering triglycerides without raising LDL and possibly decreasing the risk of cardiovascular disease. I thought their claims were quackery and my mission was to disprove the science. As I started researching as many Omega 3 studies which I could get my hands on, I noticed that EPA acted much differently that DHA or a mixture of Omega 3's. Most of these research papers studied biomarkers but one thing was evident - EPA has a **potent** anti-inflammatory effect as one of its modes of action. I was confident that Reduce-It would be successful when they reported their findings but my research had its overall effects around 17-18%. Even I had underestimated the benefits of EPA's effectiveness on lowering CVD. I continue to study the effects of EPA and the science continues to strongly support Amarin's claims. EPA's effects are not a fluke or anomaly. I am currently considering ways that EPA can be utilized in my field of veterinary medicine to benefit my patients with pancreatitis and inflammatory conditions.

[redacted]

[redacted]
Senior Software Engineer
Citizen/Resident of the United States
Family history of heart disease. Prescribed Vascepa over 3 years ago. I am a believer in the science and clinical benefit of this drug.

[redacted]

[redacted]
MBA International Business
Citizen/United States of America
Family history of heart disease. Father passed away age 50 from heart attack. Mother died from hypertrophic cardiomyopathy. Prescribed Vascepa 10 years ago for lowering Tg and more recently for CV risk reduction. I feel 1000 percent better when I'm on Vascepa. In many ways hard to explain. Better total cardio output.

[redacted]

[redacted]
IT Security Systems Manager
Citizen/Dutch
Resident/Switzerland
Family history of heart disease. Lost my sister, age 63, from a heart attack.

[redacted]

[redacted]
Aircraft Maintenance Technician

Citizen/United States of America
Family History of Heart disease
[redacted]

[redacted]
Operations Coordinator/ Current Premed Student NVCC
Citizen/ United States of America
Family history of heart disease. I've lost both maternal grandparents to strokes before they reached 74. Outside my bloodline, my brother-in-law almost died from a "widow maker heart attack" last year. I am currently working with him to gather the evidence through widely available literature to have him prescribed Vascepa, as well as my mother (76) who lost both of her parents to CVD. The sheer amount of clinical research evidence of Vascepa's ability to not only lower inflammatory markers, promote plaque regression and improve endothelial repair, outside of simply lowering triglycerides, is why I advocate my loved ones have access to Vascepa for its absolute cardiovascular benefit.
[redacted]

[redacted]
Statistician
Citizen/United States of America and Belgium
MA Columbia University, B.Sc. Vesalius College
I trust the science and know several people who could benefit from Vascepa
[redacted]

[redacted], Amarin
BS-Business/Biology
Citizen/United States of America
As a former Amarin employee, I not only believe in the science, I know the science of Vascepa/Vazkepa is sound. I am privy to many physicians who have witnessed the benefit of Vascepa. The time, effort, and money put into all the research conducted thus far has shown the superiority of Vascepa. As an adjunct to statin therapy the results (RRR) are incredible and the ARR reductions are astounding. It is not often the medical community discovers a drug that does what Vascepa/Vazkepa does and every patient in the world should have the opportunity to take it especially with its low side effect/adverse event profile. The totality of the abundance of research has proven Vascepa's right to be approved. I have always had high cholesterol with historical records in the early 80's and have been on every major statin drug available since the early 90's, now 10 mg rosuvastatin. My cholesterol history is from 300-350 mg to 160-170 mg at present. The problem is hereditary; my Dad had a triple bypass at Cleveland Clinic in 1974 and trundled along for another 18 years. My heart had a stint with atrial flutter in March 2014 wherein an ablation was done. I have had 2 minor flutter flare ups in the ensuing 8 years but nothing of importance. I started V in May 2014 based on the flutter incident. My experience since starting Vascepa with a Statin. Cholesterol - 165 mg +/- 5 mg, EPA/AA ratio - 1.0 - 1.5 HDL - 50 – 80, LDL - 95 – 135, Total cholesterol 160 – 170. Rosacea - Recurring on nose - gone after less than 2 months of V. Dry Eye - Left eye, recurring problem even with drops - gone in less than 2 months

[redacted]

[redacted]
Professional Firefighter/Emergency Medical Technician
BA Sociology SUNY @ Purchase
Citizen/United States of America
All people of the world deserve access to this miracle drug that enhances quality and longevity of life.
[redacted]

[redacted] Allstate Ins. Co.
U.S. citizen and domiciliary.
In 2002 I had 2 stents implanted in two heart arterial blockages and went on statins. In 2015 I was diagnosed with 3 more blockages, one 100% but revascularized and 2 80% but un-stentable. Open heart surgery was recommended, but I declined, in favor of a regimen of Vascepa and Repatha. My current condition is greatly improved, no chest pains, no shortness of breath—in short, a sense of health and well-being. Given my English heritage, I would hope my British friends would all have ready access.to these amazing drugs.
[redacted]

[redacted]
Retired
University graduate
South Hamilton, Massachusetts USA
Longtime (Over a dozen years) supporter and investor in the development of Vascepa/Vazkepa
by Amarin and the designers of the Reduce-It study by Dr. Deepak Bhatt et al. Firm believer in EPA's
potential for further development in prevention and mitigation of indications beyond just its
overwhelming efficacy and cost effectiveness in cardiovascular disease, as stated in the independent non-profit October 2019 Institute for Clinical Review (ICER) report. While currently in good health, I hope I and many others can have the option to benefit from widely Available and accessibility of Vascepa/Vazkepa.
[redacted]

[redacted]
Real Estate Investor
Business Management Magna cum Laude
USA
I'm supporting this response because I want the drug to have the most exposure to save lives.
[redacted]

[redacted]
USA
[redacted] Georgia-Pacific
BA in Psychology from SUNY, Albany

I am a VASCEPA® patient. I have hemochromatosis and VASCEPA® has improved my ferritin and iron levels. Both my father and father-in-law died from heart attacks. I hope to avoid such a fate by taking VASCEPA®.
[redacted]

[redacted]
USA
BS and MS degree (Georgetown for NP)
NP, (NICU) RN license for NYS, NP license for NYS
I strongly believe in the health benefits of Vascepa (EPA) which go much further than what is currently known.
[redacted]

[redacted]
Senior Account Executive, Sales
USA
B. Bus. Sc.
I Had a friend, business peer, with triglycerides over 500. He and his doctor extremely happy with quick reduction in triglycerides. A sales rep who had a problem staying awake during meetings, (reprimanded at least once), and a general lack of energy. After a few months on Vascepa, never dozed off during any meetings and went from average sales rep to one of the best in the company, far more energetic and focused.
[redacted]

[redacted]
Retired Stock Analyst
USA
Monmouth University
My optometrist recommended I take fish oil after cataract surgery for healing purposes. I tried OTC fish oil but had bad taste, smell and upset my stomach. I found Vascepa when I was researching Amarin Pharma as an investment. When I had my annual checkup I asked my GP if she knew of Vascepa and since my family had a history of heart disease and explained that my optometrist recommended "fish oil" could she write me a script, she had no problem for reasons explained. Then I went for my annual checkup with my cardiologist he was thrilled that I was on Vascepa, he was my mother's cardiologist before she passed so he knew of her heart issues.
[redacted]

[redacted]
USA Citizen
Vascepa Patient
I have personally taken Vascepa for four years, as an adjunct to diet and exercise. I began taking Vascepa in my late 20s as I saw early signs of CVE risk factor (etc. Trigs and LDL cholesterol rising, heart arrhythmia, and weight gain), despite a low carb diet, fasting, and exercise. Since taking Vascepa, my labs are suggesting my risks of having a CVE have decreased, the arrhythmia has gone away, and general inflammation has been reduced. The science of Vascepa is supported by numerous studies and has been vetted by many world health organizations. The theory of mineral oil skewing Vascepa success has been proven to be a non-factor. Additionally, the cost benefit analysis for implementing Vascepa as a treatment option is strong. What does it cost to treat a CVE

death? Think of this not just from the medical treatment perspective, but from lost production and from the lost utility of friends and/or family of the deceased. What is in the annual cost of Vascepa? Multiple pharmacoeconomic studies have shown Vascepa to have substantial value over its retail cost. A vote to deny Vascepa's approval in the U.K. is a vote for sustaining the level of deaths by CVE in the U.K.
[redacted]

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Icosapent ethyl for the treatment of hypertriglyceridaemia [ID3831] – ERG critique of ACD response

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 01/03/22

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number STA 13/42/04.

Declared competing interests of the authors

None.

Acknowledgements

None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Armstrong N, Grimm S, Ramaekers B, Essers B, Wijnen B, O'Meara S, Ryczek E, Noake C, Wolf R, Joore M, Kleijnen J. Icosapent ethyl for the treatment of hypertriglyceridaemia [ID3831]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2021.

Contributions of authors

Nigel Armstrong acted as project lead, health economist and systematic reviewer on this assessment, critiqued the clinical effectiveness and cost effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Ben Wijnen and Brigitte Essers acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Robert Wolf, Susan O'Meara and Edyta Ryczek acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

ABI	Ankle-brachial index
AE	Adverse events
AIDS	Acquired immunodeficiency syndrome
AIC	Akaike information criterion
ALT	Alanine aminotransferase
Apo B	apolipoprotein B
ASCVD	atherosclerotic CVD
AST	Aspartate aminotransferase
BCS	Best case scenario
BI	Budget impact
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CAD	Coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Clinical Guideline
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CrCL	Creatine clearance
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTR	Clinical trial results
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
DMC	Data monitoring committee
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EMA	European Medicines Agency
EPA	Eicosapentaenoic acid
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPA	Eicosapentaenoic acid
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FAD	Final appraisal document
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FE	Fixing errors

FV	Fixing validations
GHS	Global health status
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
hsCRP	high-sensitivity C-reactive protein
hsTnT	high-sensitivity troponin T
HSUV	Health state utility value
HTA	Health technology assessment
IC	Indirect comparison
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost effectiveness ratio
ICF	Informed consent form
IDFS	Invasive disease-free survival
IFCC	International federation of clinical chemistry
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
JELIS	Japan EPA Lipid Intervention Study
KSR	Kleijnen Systematic Reviews
LDL-C	Low-density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
LYs	Life years
LYG	Life years gained
MACE	Major adverse cardiovascular event
MAIC	Match-adjusted indirect comparison
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MJ	Matters of judgement
MOS SF-36	Medical Outcomes Study Short Form Survey
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NLM	National Library of Medicine
NMA	Network meta-analysis
NR	Not reported
NYHA	New York Heart Association
ONS	Office for National Statistics
OS	Overall survival
partSA	Partitioned survival analysis
PAS	Patient access scheme
pCR	Pathological complete response
PFS	Progression-free survival
PH	Proportional hazards
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVD	Peripheral vascular disease
Q3W	Every three weeks
QALY	Quality adjusted life year
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial
RLP-C	Remnant lipoprotein cholesterol
RR	Relative risk; Risk ratio
SAE	Serious adverse events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
STEEP	Standardised definitions for efficacy endpoints
TA	Technology assessment
TC	Total cholesterol
TEAE	Treatment emergent adverse events
TG	Triglyceride
TIA	Transient ischemic attack
tpCR	Total pathological complete response
TSD	Technical Support Document
TTO	Time trade-off
TTOT	Time-to-off treatment
UK	United Kingdom
ULN	Upper limit of normal
UMC	University Medical Centre
USA	United States of America
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization
WOSCOPS	West of Scotland Coronary Prevention Study
WTP	Willingness-to-pay

Table of Contents

1. *General comment / cover letter*

This is an introduction to the specific comments in the company response to the ACD, to which the ERG will respond below.[1]

2. *Icosapent ethyl is likely to be used mostly in a primary care setting*

This is a statement by the company and therefore requires no comment from the ERG.

3. *Generalisability of the REDUCE-IT trial results to the NHS in England*

The company presented a comparison between REDUCE-IT and two additional studies, one Canadian and the other French. The ERG considers that these studies add very little to the comparison the English NHS experience.

The company also argued that there would be no effect on the treatment effect of icosapent ethyl on CVD event rate of PSK9 inhibitors being excluded from the REDUCE-IT trial. In support, they cited an observational study of 18 European countries that estimated use of PCSK9 inhibitors to be 1.1% "*with established ASCVD*" and NICE guidance on PCSK9 inhibitors that stated that reimbursement was restricted to *"high and very high-risk patients with LDL-C persistently above 3.5mmol/L, in case of alirocumab and evolocumab, and above 2.6mmol/L in the case of inclisiran".* They also argued that "*the mechanism by which icosapent ethyl lowers CV risk is independent of LDL-C"* The ERG consider that it is unlikely that, if the rate of CV events was reduced by PSCK9 inhibitors that this could not affect the treatment effect of icosapent ethyl, although the size of this impact is probably small if PSCK9 inhibitor use is low.

4. *Icosapent ethyl's mechanism of action*

The company stated the mechanism of action in terms of reduction of CV events is "not completely understood". This also relates to the challenge in explaining the treatment effect observed in the REDUCE-IT trial and the hypothesis that a harmful effect of the mineral oil placebo might be partly responsible (see Comment 5.).

5. *Mineral oil placebo in REDUCE-IT*

The company argue that a reduction in treatment effect die to the harmful effect of the mineral oil used as placebo of 7-13% suggested by the committee is implausible and that any plausible reduction should be no more than 3%. No additional evidence was presented by which any decrease in treatment effect might be estimated. Therefore, despite some reservations by the ERG regarding the basis of the 7-13% reduction suggested by the committee, as expressed in the ERG critique of the company Technical Engagement response, it does seem reasonable to consider such a reduction in scenario analyses.[2]

6. *Low rate of eructation / unpleasant burps with icosapent ethyl*

The company presented evidence that suggested a low rate of eructation generally and a lower rate of withdrawal in the icosapent ethyl arm.

7. *Model structure*

The company did not provide any additional evidence to justify the model structure, apart from the validation model that is dealt with in issue 12.

The company furthermore stated: *"Amarin are not aware of any external UK datasets that could be used to estimate the baseline risk, therefore the placebo arm of the REDUCE-IT trial was used."*

Hence, no further information was provided.

8. A similar trend in results is observed for each individual component of the 5-point MACE

The company presented hazard ratios (HRs) for each component outcome of the composite 5-point MACE outcome, the point estimates for which were all [redacted] that of the composite and the 95% confidence intervals of which were [redacted] except that for nonfatal stroke, which had an upper bound of [redacted]. The company also supplied a Kaplan-Meier (KM) plot and a plot of HR versus time for each component outcome. These plots were of a similar shape to those of the composite, although it did appear that there was some variation in the pattern of change in treatment effect over time between outcomes and the composite. In particular, although there seemed to be some separation of KM curves before one year for the composite, there seemed to be no separation of curves for CV death, non-fatal MI and non-fatal stroke until about two years, one year and one year respectively. Therefore, although according to a single HR there appears to be little difference between the components and the composite, there might be a difference in the pattern of change of the HR over time. Given that the three outcomes where there appeared to be more of a lag in curve separation probably would have the most profound effect of all component outcomes, effectiveness using a composite outcome only might produce a bias in favour of icosapent ethyl in the size of the effect on patient health in the first one to two years of treatment.

9. Full time to event analysis is provided for the secondary prevention subgroup and validated by UK clinical experts as well as against an external validation model

Time to event analysis for the secondary prevention subgroup

The company provided a full assessment of the proportional hazard assumption in the secondary prevention subgroup, and concluded that fitting dependent extrapolation models was most appropriate. The ERG agreed with this assessment.

The company fitted the standard parametric survival models and assessed goodness of fit statistics. The ERG notes that for the first event, goodness of fit was not reported for the Weibull distribution (Company's Table 4 in ACD response). The company had mentioned an error that occurred when fitting the Weibull in the ITT population, but claimed this was resolved in the secondary prevention subgroup. The ERG would like clarification for this. It is currently not possible to assess the Weibull distribution in terms of its statistical fit.

For the first event, the ERG considers that based on statistical fit, it is difficult to rule out any of the distributions, apart from perhaps the lognormal, which is inferior. All distributions showed a reasonable fit with the REDUCE-IT KM data at 5 years, as reported in Table 5 of the company's ACD response. However, it should be noted that all distributions slightly over-estimated the proportion of patients with a first event in the icosapent arm, whilst for the comparator arm all distributions slightly under-estimated the proportion of patients with a first event at this time point. The company also provided a comparison with the validation model, which showed that estimated proportions of patients with a first event were broadly similar between the two models, although there was greater variability between the different distributions as time progressed (as expected). The distributions producing estimates most in line with the validation model at 20 and 30 years were the exponential, Weibull and the Gompertz models. However, there is the caveat that it is unclear to what extent this comparison should be used as informing model choice here. In terms of clinical plausibility, clinical experts recommended using the distributions with the best statistical fit. The company therefore chose the exponential.

For the second event, similarly, differences between goodness-of-fit statistics are not large and it is difficult to rule any of them out purely based on these statistics. While the company did not provide the proportions of patients with an event at 5 years as observed in REDUCE-IT (this may still be useful to appreciate smaller differences), based on visual inspection (Figures 22-23), all distributions fit the data reasonably well. The company also provided a comparison with the validation model, which showed that estimated proportions of patients with a second event were broadly similar between the two models (with the notable exception of the Gompertz), although there was greater variability between the different distributions as time progressed (as expected). The distributions producing estimates most in line with the validation model at 20 and 30 years were the exponential and log-logistic models. However, there is the caveat that it is unclear to what extent this comparison should be used as informing model choice here. In terms of clinical plausibility, clinical experts recommended using the distributions with the best statistical fit. The company therefore chose the exponential.

For the third event, based on statistical fit, the log-logistic, Gompertz and lognormal should be prioritised. The generalised gamma should be ruled out based on an implausible shape in both arms that did not fit the KM data [redacted]. While the company did not provide the proportions of patients with an event at 5 years as observed in REDUCE-IT (this may still be useful to appreciate smaller differences), based on visual inspection (Figures 24-25), all distributions but the generalised gamma fit the data reasonably well. The company also provided a comparison with the validation model, which showed that estimated proportions of patients with a third plus event were broadly similar between the two models (with the notable exceptions of the Gompertz and generalised gamma), although there was greater variability between the different distributions as time progressed (as expected). The distribution producing estimates most in line with the validation model at 20 and 30 years was the exponential. However, there is the caveat that it is unclear to what extent this comparison should be used as informing model choice here. In terms of clinical plausibility, clinical experts recommended using the distributions with the best statistical fit. The company therefore chose the exponential. The ERG notes that at 10 years only approximately [redacted] of patients (in the icosapent and BSC arms respectively) would experience a third plus event and at 20 years approximately [redacted] of patients (in the icosapent and BSC arms respectively), when using the exponential and would recommend discussion of this with clinical experts.

In conclusion, if the company's model structure is accepted, the company's time-to-event analysis appears appropriate. There is still uncertainty about the most appropriate extrapolation model especially for second and third plus events, however, company's scenario analyses show that the choice of distribution for the second and third plus events has minimal impact on the ICER.

Comparison of mortality in trial and as estimated in company's model

A comparison of overall mortality from the REDUCE-IT trial to overall mortality estimated from the company cost-effectiveness model showed some discrepancies. The company attempted to resolve these by replacing the general population background mortality used in the model by mortality estimates from which the CV specific mortality estimates were removed. While this approach appears valid, the company has not provided information to show how the overall mortality estimated from the company model changed as a result of this adjustment. The company did mention *"remaining discrepancies between the overall mortality in the REDUCE-IT trial and the cost-effectiveness model"*. According to the company, these could likely be attributed to the controlled environment of a clinical trial setting and the company's experts confirmed that this may be the case. The magnitude of these remaining discrepancies is, however, unclear. Furthermore, all three UK clinical experts believed that the survival

estimates produced from the model were similar to what they would expect to observe in UK clinical practice. The ERG recommends that the mortality estimates after this adjustment be displayed in the same Table 11. This would allow an assessment of whether this concern was addressed and whether the company's explanation for any remaining discrepancies is plausible. Furthermore, the ERG explored disabling all-cause mortality in the model in a scenario, as this is likely already captured in the follow-up of the trial. The resulting modelled mortality estimates for placebo are then exactly in line with mortality observed in the trial at year 1 – however, there is a large discrepancy at 5 years.

There may be at least two mechanisms in the model by which mortality is wrongly estimated, for example, by over- or under-estimating first, second or third plus event rates or by assuming that the distribution over the 5-point MACE events remains constant over time (regardless of number of events a patient has had).

10. The evidence and expert input available do not support the application of a treatment waning effect

The company did not apply treatment waning in their new revised base-case. The company justified this by stating: *"Including all patients that were randomised to icosapent ethyl means that within the clinical efficacy curves estimated, any efficacy lost due to discontinuation is accounted for."* The ERG notes that doubts remain over long-term treatment effectiveness, especially considering the high long-term discontinuation rates. The company also cited expert opinion and assumptions of no treatment waning in previous appraisals to support the exclusion of treatment waning from the base-case. However, the ERG considers that a comparison with previous appraisals is of little value if not also comparing the discontinuation rates and observed treatment effects in those settings. The ERG thus considers the missing link between treatment discontinuation and loss of effectiveness as unresolved in the base-case.

In scenarios, the company implemented treatment waning at 10 and 20 years, assuming that at those points the hazard rates of the comparator apply only for those patients that had discontinued treatment at that point. Because of the model structure (where patients that had their first event move to the second event curve and after that to the third plus event curve), a proportion of patients in these scenarios move immediately from (in the worst case) having had no event at all to having had three plus events, an assumption that would lack face validity. The company did not provide details on the proportion of modelled patients that would be affected by this, so it is difficult to judge how impactful this would be. Perhaps the company could provide an indication of this. The company claims that for this reason, the treatment waning scenarios under-estimate the effectiveness of icosapent ethyl.

In another way, the ERG considers that these scenarios may continue to over-estimate the effectiveness of icosapent ethyl. It may be a valid assumption to think that icosapent ethyl ceases to have an effect at an individual level once it is discontinued. A reasonable implementation of loss of treatment effect may then be to move patients to the placebo effectiveness right after the end of trial follow-up instead of after 10 or 20 years. Perhaps this scenario could be provided by the company.

It is very difficult to know where the truth lies, also considering the above-mentioned caveats around the implementation of the model and implications for treatment waning. The ERG considers that a no treatment waning scenario can be considered for decision-making, possibly as a lower bound to the ICER, while the 10 year treatment waning scenario may be considered as an alternative, perhaps not quite upper bound to the ICER.

11. Full analysis for time to treatment discontinuation (TTD)

The company provided updated TTD time to event analysis in the subgroup. The chosen distribution was the Weibull, which had the best statistical fit. Overall, the choice of distribution does not seem to have a major impact anymore, according to the scenarios presented in Table 17. However, a scenario using the gamma distribution was not provided, even though it had the second-best statistical fit. The ERG explored a scenario using this distribution.

12. Evidence that diabetes and number of previous events are non-CV related death modifiers

The company presented the opinion of three UK clinical experts and a summary of several studies that showed an effect of diabetes and previous CV events on non-CV related mortality. This suggests that there is evidence of an effect on non-CV death, although a more reliable estimate of the size of this effect would require a systematic review.

13. The company's model has been further validated with an external model developed for icosapent ethyl

The company has not provided more detailed information on what went wrong in the original cross validation model and how it was fixed in the updated cross validation model. The company continued to state: *"At the technical engagement stage, it was noted that there was a discrepancy in the way the proportion of patients experiencing each type of event were calculated for the cross-validation model. Rather than calculating the proportions based on the total cohort entering the model, the proportions were calculated based on the number of patients left in the model each year."* This precise phrasing was used in a previous document and the ERG had then noted that this was insufficient information and had requested additional detail, which was again not provided. Without more context, it is difficult to know whether calculating the proportion of patients experiencing an event based on number of patients left in the model each year would be wrong – the ERG also wonders why each year when the cycle length in the validation model was 6 months, and was curious what was meant by *"left in the model"*.

If one accepts this correction, results of the company's and cross-validation models are indeed more comparable. The largest discrepancy occurs in the third plus event rates, which have a lower impact on overall model outcomes. This means that ICERs are now fairly comparable between the two models.

14. Revised economic analyses for the subgroup of patients in secondary prevention

Model amendments have been checked by the ERG.

ERG analyses

Table 1: ERG analyses in the secondary prevention population (deterministic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base-case							
Icosapent Ethyl	£23,693	11.587	8.361	£9,723	0.385	0.490	£19,848
Placebo	£13,970	11.201	7.871				
ERG base-case: treatment waning upon treatment discontinuation at 10 years							
Icosapent Ethyl	£23,862	11.526	8.309	£9,892	0.325	0.438	£22,609
Placebo	£13,970	11.201	7.871				
Scenario 1: treatment waning upon treatment discontinuation at 5 years							
Icosapent Ethyl	[redacted]	11.479	[redacted]	[redacted]	0.278	[redacted]	£26,228
Placebo	[redacted]	11.201	[redacted]				
Scenario 2: all-cause mortality disabled							
Icosapent Ethyl	[redacted]	18.144	[redacted]	[redacted]	0.302	[redacted]	£19,371
Placebo	[redacted]	17.842	[redacted]				
Scenario 3: treatment effect reduction of 7%							
Icosapent Ethyl	[redacted]	11.526	[redacted]	[redacted]	0.216	[redacted]	£34,067
Placebo	[redacted]	11.310	[redacted]				
Scenario 4: treatment effect reduction of 13%							
Icosapent Ethyl	[redacted]	11.526	[redacted]	[redacted]	0.123	[redacted]	£55,465
Placebo	[redacted]	11.403	[redacted]				
Scenario 5: TTD gamma distribution							
Icosapent Ethyl	[redacted]	11.523	[redacted]	[redacted]	0.322	[redacted]	£22,472
Placebo	[redacted]	11.201	[redacted]				
Scenario 6: Company base-case but with 7% treatment effect reduction							
Icosapent Ethyl	[redacted]	11.587	[redacted]	[redacted]	0.262	[redacted]	£29,832
Placebo	[redacted]	11.324	[redacted]				

1. REFERENCES

[1] National Institute for Health and Care Excellence. *Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]: consultation on the appraisal consultation document* London: NICE, 2022 [accessed 23.2.22]. 54p.

[2] Armstrong N, Grimm S, Ramaekers B, Essers B, Wijnen B, O'Meara S, et al. *Icosapent ethyl for the treatment of hypertriglyceridaemia [ID3831]: a Single Technology Assessment.* York: Kleijnen Systematic Reviews Ltd, 2021