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:

1. **Response to consultee, commentator and public comments on the Second Appraisal Consultation Document (ACD)**

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

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

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

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

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Amarin	**General comment / cover letter** Dear Appraisal Committee Members, Amarin welcome the opportunity to comment on this Appraisal Consultation Document (ACD), and kindly ask the committee to reconsider its recommendation published in the ACD in light of the additional clarifying evidence provided. Cardiovascular disease (CVD) is the leading cause of death in the UK.[1] Despite traditional risk factor control in patients with established CVD, it is estimated that more than a third of patients will experience a major adverse cardiovascular (CV) event within 5-7 years.[2] There are 6.7 million people living with CVD in England and Wales and the annual cost to the National Health Service (NHS) is more than £9 billion per year. The coronavirus pandemic (COVID-19) has exacerbated CVD healthcare burden, resulting in an estimated 50,000-100,000 excess CVD deaths in England during the pandemic.[3] The NHS Long Term Plan regards CVD as '*the single biggest area where the NHS can save lives over the next 10 years*'. The plan explicitly aims to prevent 150,000 heart attacks, strokes and vascular dementia cases by 2029, in order to improve CV mortality. It is estimated that a further 12,000 avoidable heart attacks and strokes will occur by 2025, if missed opportunities for treatment initiation due to the coronavirus pandemic are not addressed. This highlights the urgent need for a treatment that can reduce the risk of CV events and reduce CV mortality rates for years to come. Currently there are no specific treatments available to lower CV risk in adult statin-treated patients with established CVD, elevated serum triglycerides (1.69 to 5.63 mmol/L) and controlled LDL-C.	Thank you for your comments. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			The REDUCE-IT trial demonstrated that icosapent ethyl significantly reduces major adverse CV events in adult statin-treated patients with established CVD and elevated triglycerides (1.69 to 5.63 mmol/L).[4] On this basis, the European Society of Cardiology (ESC) guidelines recommend to consider '*icosapent ethyl (2x2g/day) in combination with statins'* for the treatment of hypertriglyceridemia in high CV risk patients.[5] Amarin have sought to address the concerns raised by the committee, which will reduce the uncertainty in making a recommendation. This includes: • Input from nine UK clinical experts from a recent medical advisory board indicating that the data from the REDUCE-IT trial would be generalisable to the UK population. This compliments the previously supplied observational studies of established CVD patients by Steen 2017, Lawler 2020 and Ferrières 2020, showing broadly similar baseline characteristics between the trial and Steen cohorts as well as similar CV risk between the trial and the Western European populations.[6–8] • Three additional within-trial analyses conducted by the company quantifying the hypothetical effect of elevations in hs-CRP and LDL-C on the placebo arm of the REDUCE-IT trial, which further demonstrate that the maximum theoretical effect of placebo on the relative benefit of icosapent ethyl is approximately 1.5%. • Validation of the clinical outcomes estimated by the economic model by three UK clinical experts. A cross-validation was also undertaken with an external published, peer reviewed Markov model, to compare the clinical and economic outputs with the company model.[9] • Additional evidence to justify why no treatment waning should be applied to patients discontinuing icosapent ethyl. Amarin also would like to highlight our concern to the committee that 'uncertainty' in this appraisal is taken into account twice in defining NICE's preferred incremental cost-effectiveness ratio (ICER) – once to justify lowering the willingness to pay threshold from £30,000 to £20,000 per QALY (a *de facto*	

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			up to 33% reduction in the commonly used acceptable ICER threshold set by NICE), and a second time in suggesting a treatment waning effect and in reducing the relative efficacy of icosapent ethyl vs. placebo. This is considered by the company as a disproportionate application of uncertainty adjustment tools by NICE. Attempting to take into account for a proportionate application of any residual uncertainty remaining after the additional evidence provided, Amarin have submitted a revised company base case. Changes to the company base case are as follows: application of no treatment waning, a maximum hypothetical effect of placebo of 1.5% relative reduction in treatment effect, and a revision of the list price of icosapent ethyl from £173.00 per pack of 120 capsules, to £[redacted] A detailed summary of all the uncertainties raised by the committee and how these have been addressed can be found in sections 1 – 10. All new evidence has been provided in the appendix at the end of this document.	
2	Company	Amarin	**The population in REDUCE-IT is generalisable to the NHS in England** In section 3.6 of the ACD, it was noted that: "*The population in REDUCE-IT may not be generalisable to the NHS in England"*. The company has already provided the committee with multiple lines of evidence from populations analogous to the UK population including France, Canada and the UK, indicating similarities in baseline characteristics and levels of residual CV risk.[6–8] In addition, an advisory board conducted by Amarin on 24th March 2022, including nine UK clinical experts from the specialties of cardiology, diabetology, chemical pathology and general practice, supported the view that the data from REDUCE-IT would be generalisable to the UK population. Clinical experts indicated that there is no reason to believe that the results of REDUCE-IT would not be applicable to UK clinical practice. In section 3.7 of the ACD, it was noted that: "*The committee concluded that the current management of cardiovascular*	The committee considered that there was an increase in uncertainty in the trial results because the trial population may not fully represent NHS clinical practice. See FAD section 3.6.

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			disease and diabetes is not fully reflected in REDUCE-IT, so the generalisability of the trial results is uncertain". The company wishes to reiterate that usage of agents such as SGLT2 inhibitors and GLP-1 agonists was consistent with the time-period over which the REDUCE-IT trial was enrolling patients ([redacted]% and [redacted]%, respectively). Furthermore, patients who are not diabetic would not necessarily be eligible for treatment with these agents, and no statistically significant interaction for the efficacy of icosapent ethyl was observed in the REDUCE-IT trial when comparing patients with and without diabetes at baseline (HR 0.77 vs. 0.73, P_{int} = 0.56).[4] The use of PCSK9 inhibitors is not relevant to this appraisal as patients eligible for icosapent ethyl have LDL-C levels below 2.6 mmol/L as per the trial inclusion criteria. Patients in England and Wales are only eligible for PCSK9 inhibitors (alirocumab, evolocumab) when LDL-C levels are above 2.6 mmol/L (NICE TAs 393, 394, 733).[10–12]	
3	Company	Amarin	**Icosapent ethyl's mechanism of action** In section 3.8 of the ACD, it was noted that: "*The committee concluded that the mechanism of action for icosapent ethyl is not fully understood, which adds uncertainty to the trial's results"*. The committee's position that a lack of certainty about the mechanism of action of icosapent ethyl creates uncertainty in the results of the REDUCE-IT trial is not clinically relevant to the interpretation of the overall outcomes measurement. During a recent medical advisory board, UK clinical experts remarked that a well-understood mechanism of action is not a requirement for clinical use, and many drugs available to prescribe have unknown mechanisms of action and have been highly beneficial for patients. For example, metformin, SGLT2 inhibitors and GLP1 agonists. In addition, preclinical studies have identified several modes of action that support a role for EPA, the active drug of icosapent ethyl, in beneficially	The committee considered that the mechanism of action not being understood added uncertainty to the trial's results because the difference in benefit compared with STRENGTH had not been fully explained. See FAD section 3.7.

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			altering the development, progression, and stabilisation of atherosclerotic plaque. These include 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.[13] The atheroprotective mechanisms exerted by EPA are further discussed by Mason PR *et al.,* and the committee is referred to this publication.[14] It is worth noting that additional clinical studies of icosapent ethyl have confirmed effects on reducing coronary atherosclerotic plaque volume.[15,16] Ongoing research by different groups will further explain the pleiotropic effect of icosapent ethyl in the upcoming years. Section 3.8 of the ACD also states: *"…that the reduction in cardiovascular risk observed in REDUCE-IT was larger than what would be expected from a reduction in triglycerides alone."* The company wishes to point out this is entirely consistent with what is known about icosapent ethyl. Post-hoc analyses of the effects of variations in baseline or achieved triglyceride levels on the benefit of icosapent ethyl vs. placebo in the REDUCE-IT trial have not demonstrated any interactions (Figure 2 and Figure 3). The European Medicines Agency (EMA) also concluded in its assessment of icosapent ethyl that *"TG reduction appears to provide only a minor contribution to the reduction in risk of cardiovascular events with icosapent ethyl*."[17]	
4	Company	Amarin	**Mineral oil placebo in REDUCE-IT and difference in results between the REDUCE-IT and STRENGTH trials** In section 3.9 of the ACD, a professional group and the NHS England clinical adviser have commented that: "…*mineral oil may not be a true neutral oil and may have increased the risk of cardiovascular events in the placebo group. This would exaggerate the observed difference in cardiovascular events between the icosapent ethyl and placebo groups."* The company rejects this conclusion on the grounds that there is no evidence	The committee concluded that the relative effect of icosapent ethyl was uncertain because of the potential negative effect of the mineral oil placebo. See FAD section 3.8.

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			to suggest that mineral oil is not a true neutral oil, or that it increases the risk of CV events. The observed changes in biological parameters in the REDUCE-IT trial are in-line with placebo changes observed in 79% of CV outcomes trials conducted between 2003-2019, that did not employ mineral oil as placebo.[18] This includes the placebo arms of other trials involving other compounds recently appraised by NICE such as alirocumab (Figure 4). More plausible explanations for these changes include regression to the mean effects after study inclusion and natural history of the disease, as noted by the regulatory authorities. The safety of mineral oil is generally inferred from a long history of use with limited adverse effects and from use as placebo in other clinical studies. A systematic review of the literature including 80 studies that utilised mineral oil as placebo did not demonstrate directionally consistent effects on parameters such as triglycerides or LDL-C, including in the subgroup of studies on patients with established CVD or diabetes.[18] The placebo in the REDUCE-IT trial was composed of pharmaceutical-grade, light-mineral oil, comprising straight-chain n-alkanes 15-26 carbon atoms in length.[18] This was manufactured under Good Manufacturing Practice conditions identical to other investigational medicinal products used in clinical trials. It was selected as the most appropriate placebo after discussion with regulatory authorities. Structurally, pharmaceutical-grade mineral oils (straight-chain n-alkanes) are not dissimilar to commonly consumed saturated and unsaturated fatty acids, including the polyunsaturated, monounsaturated and saturated fatty acids present in corn oil, e.g. stearic and linoleic acid.[19] In section 3.9 of the ACD, 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 company rejects this conclusion of similarity on the grounds that different	

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			active compounds were investigated in the REDUCE-IT and STRENGTH trials. Regulatory authorities have made clear statements distinguishing icosapent ethyl, a pure EPA compound, from other mixed omega-3 preparations containing EPA and DHA. The Committee for Medicinal Products for Human use (CHMP) considers icosapent ethyl to be *"a new active substance as it differs significantly in properties with regard to efficacy from known mixture of 'omega-3-acid ethyl esters 90' contained in medicinal product(s) previously authorised within the European Union".*[17] Therefore, it is unreasonable for the committee to conclude similar results from these CV outcomes trials should be expected. Numerous CV outcomes trials examining the effects of mixed omega-3 (EPA / DHA) compounds have failed to show any CV benefit.[20–22] In contrast, two large CV outcomes trials of icosapent ethyl have shown statistically significant benefits in reducing CV events over a median five years of follow-up; one of which, the JELIS trial, was not performed against a mineral oil placebo.[4,23] Several lines of evidence indicate that EPA and DHA have distinct tissue distribution patterns, cell membrane locations and distinct physiologic functions as a consequence of differing carbon chain lengths (22 vs. 20) and number of double bonds (6 vs. 5). Additionally, laboratory studies suggest when EPA and DHA are combined in equal amounts, the membrane effects of both are attenuated, suggesting EPA & DHA have counter-regulatory actions.[24] A meta-analysis of randomised placebo-controlled trials of monotherapy with EPA, DHA, or EPA vs. DHA has also demonstrated different effects on lipid parameters including LDL-C, HDL-C and triglycerides, which have established clinically relevant relationships with CV outcomes.[25]	
5	Company	Amarin	**It is not appropriate to consider scenarios for an estimated reduction in treatment effect from 3% to 10%** In section 3.9 of the ACD, it is stated that: *"…the committee concluded it would be appropriate to consider scenarios estimating a reduction in treatment effect from 3% to 10%, based on the discussion in the EPAR. The committee considered the scenario using around 7% in its preferred analysis because it was near the middle of the range and*	Considering the company's analyses and the conclusion of the European Medicines Agency, the committee concluded that it would be appropriate to consider scenarios estimating a reduction in treatment effect from 1.5% to 3%. See FAD section 3.9.

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			aligned with Doi et al." The company rejects this conclusion for several reasons. Firstly, the committee was incorrect to state that the conclusion of the CHMP in the EPAR was 10%. The Risk-Benefit Conclusion of the CHMP taken from the EPAR is reproduced *verbatim* below: *"Taking into consideration that such effects cannot be independently summed up, in a worst-case scenario attributing all of these effects to mineral oil, a putative negative impact of mineral oil on MACE should be below 10%. However, this is still an overestimation.* *Regression to the mean effects and the natural course of the disease may considerably have contributed to the increase in LDL-C and apoB.* *Furthermore, the scenario does not consider that the increase in HDL-C could be beneficial. Analyses taking physicochemical properties of drugs, efficacy and bleeding patterns into account did not indicate a major impact of mineral oil on absorption of statins, antiplatelet drugs and anticoagulants. However, e.g. the analyses of bleeding patterns were hampered by the fact that Vazkepa itself increases the risk of bleeding. Based on analyses as provided by the applicant, a putative negative effect of mineral oil should not account for more than 0.3 – 3% of MACE events."*[17] Therefore, it should be clear to the committee that the conclusion of the CHMP is that the maximum negative hypothetical effect could be 3%. This determination is actually based on an independent covariate adjusted Cox regression analysis performed by the FDA, not by the company as stated incorrectly in the EPAR, which the company subsequently provided to the EMA. This independent analysis is described at length in the FDA Briefing Document Endocrinologic and Metabolic Drugs Advisory Committee Meeting November 14, 2019, and the company requests the committee refer to this document when making its conclusions.[26] In deference to the committee, the analysis conducted by the FDA has been independently replicated here by the company using the REDUCE-IT trial dataset.	

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			Importantly, whilst several of the biological parameters that changed in the placebo arm of the REDUCE-IT trial are correlated with CV risk, their effects are not mutually exclusive and therefore cannot be simply summed. For example, changes in LDL-C are accounted for in considering changes in non-HDL-C or apoB. Therefore, when considering the effects of these parameters on CV risk, it is only reliable to estimate the additive effects of changes in one or two of the related lipid parameters (e.g., LDL-C, and apoB) and hs-CRP, which may reasonably be considered to independently effect CV outcomes. This is the same approach taken by Doi *et al.* It is also important to account for the theoretical positive effects of the observed 5.7% increase in HDL-C in the placebo arm of the REDUCE-IT trial, and to adjust for other variables in the *within-trial* dataset known to affect CV outcomes such as age and diabetes status etc. using *within-trial* data on covariates, which could not be done by Doi *et al*. The results of the company's replication of the FDA Cox regression model, examining the effects of hs-CRP and LDL-C as covariates on the relative benefit of icosapent ethyl, both from the perspective of the maximum absolute level at year 1 for LDL-C and year 2 for hs-CRP, and the change from baseline values, including a broader range of LDL-C analysis methods than was done by the FDA, are shown in Figure 5. [redacted]27 The company has also conducted a new propensity score matched approach to the Cox regression analysis, accounting for the overlapping effects of LDL-C, hs-CRP and apoB. [redacted]	

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			[redacted][27] The company also wishes to provide the following additional evidence to support the maximum hypothetical 3% negative effect of biological parameter changes in the placebo arm. Patients in the REDUCE-IT trial underwent measurement of serum active drug concentration (EPA) annually during the trial. At the end of year 1, EPA levels increased by 393% in the icosapent ethyl arm and decreased by 13% in the placebo arm compared to baseline. An exposure response analysis was performed, including all available data points, comparing achieved EPA level with primary CV outcomes. The relationship between CV outcomes and on-treatment serum EPA was evaluated as a spline-smoothed function of on-treatment serum EPA using a Cox proportional hazard model with serum EPA as a continuous covariate, stratified by randomisation factors (CV risk stratum, geographic region, and baseline ezetimibe use), and adjusted for other potentially confounding factors including statin adherence, age, sex, baseline non-HDL-C and baseline hs-CRP. Figure 6 shows the relationship between achieved serum EPA drug level and the relative risk of the primary composite CV outcome for all patients enrolled in the REDUCE-IT trial, including placebo. [redacted] The analysis conducted by Doi *et al*., used by the committee to inform the 7% reduction in efficacy, was derived from a non-UK, Danish observational cohort. It is not a good proxy for the expected efficacy of icosapent ethyl in the UK population. Furthermore, the demographics of the Doi 2021 cohort purportedly mimicking the REDUCE-IT cohort have significant differences in terms of age,	

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			proportion of females, proportion of Caucasians, percentage diabetic, and median triglycerides (Figure 1).[17] Even with multivariate adjustment, the committee must acknowledge there will be a high degree of unmeasured confounding in the analysis that makes it a poor surrogate for the efficacy of icosapent ethyl when compared to placebo. As previously pointed out to the committee by both the company and the ERG, the Doi 2021 analysis has a number of other limitations including lack of data on statin usage over time and lack of repeated measurement of biomarkers, that make it unsuitable to inform this appraisal. It is also important to note that using a simulation from a Danish observational study to inform the base case analysis is not appropriate, considering randomised controlled trial evidence exists in the form of REDUCE-IT. In summary, based on multiple lines of evidence, supported by independent analyses by regulatory authorities, weighed against the obvious limitations of a single, retrospectively designed, observational study by Doi *et al*., the company believes the committee should accept the scientifically based determination that the hypothetical negative effect of biological parameter changes in the placebo arm of REDUCE-IT should be the midpoint of 0.3-3% of the relative benefit of icosapent ethyl; around 1.5%, which is in-line with the company's new base case.	
6	Company	Amarin	**A cross-validation model demonstrated the appropriateness of the company's model structure, showing that concerns raised in the ACD have minimal impact on clinical and economic outcomes** 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 (e.g., unable to skip or return to a previous state). The company model uses the time from randomisation to a first, second or third plus event, to ensure there are no issues surrounding crossover of the first, second or 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.	The committee concluded that the company's model remained uncertain and therefore the comparison with the validation model was uncertain. See FAD section 3.14.

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			A state-transition model in TreeAge, developed and adapted to a UK perspective by the MedStar group (published in the JAMA Network Open, from a US healthcare perspective),[9] was 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, then using a microsimulation model and data from published literature for the lifetime analysis. Despite using a different model structure and assumptions, the company's model produces very similar results to the cross-validation model, which removes uncertainty surrounding the modelling approach adopted and therefore demonstrates that the company's economic model is a suitable method for predicting clinical and economic outcomes for icosapent ethyl versus standard of care. Assumptions included in the cross-validation model satisfy the concerns raised by the ERG and NICE committee within section 3.12 of the ACD regarding the company model. The cross-validation model includes the following assumptions: 1. A traditional Markov modelling approach (validating the company's partSA modelling approach and addressing concerns regarding the assumption of independence of first, second and third plus MACE events). 2. The 5-point MACE outcome was modelled by each of the individual components (validating the company's assumption of modelling using the composite 5-point MACE endpoint). 3. A 6-month cycle length (validating the company's use of a one-day cycle length). 4. Published literature for predicting survival beyond the in-trial period (validating long term survival applied within the company's model). When comparing the two models, clinical outcomes remain consistent regardless of modelling assumptions used. For example, the proportion of individuals experiencing events and survival rates at set time points were	

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			similar between the company and cross-validation models across all assumptions tested. This demonstrates that the choice of model structure adopted by the company is appropriate, as it simulates results in line with what you would expect from a more conventional state-transition approach within this disease area. In section 3.12 of the ACD, it was noted that: *"The model appeared to overestimate mortality in both the placebo and icosapent ethyl groups in the 5-year comparison".* Three UK clinical experts consulted believed that the survival estimates produced from the model were similar to what they would expect to observe in UK clinical practice. They believed the remaining discrepancies between the overall mortality in the REDUCE-IT trial and the company model were likely attributed to the controlled environment of a clinical trial setting. The UK clinical experts consulted specifically 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. Finally, in section 3.17 of the ACD, it was noted that: *"There were still uncertainties about the company's model structure (see section 3.12)."* The company would like to clarify that the purpose of the comparison with the cross-validation model was not to further support the company base case ICER or inputs used within the model, but it was in fact to support the robustness of using an alternative modelling approach with the same set of data, and what the impact of this would be for decision making. The comparison with the cross-validation model has demonstrated that the partSA approach used in the company model is appropriate for predicting clinical and economic outcomes within this disease area.	
7	Company	Amarin	**A similar trend in results is observed for each individual component of the 5-point MACE**	The committee considered that using the composite outcome in the model increased uncertainty. See FAD section

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			In section 3.13 of the ACD, it was noted that: "*Using the composite 5-point MACE outcome in the model increases uncertainty*". 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 were provided for the secondary prevention cohort in response to the first ACD. Hazard ratios for CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, and unstable angina in the REDUCE-IT trial were presented in section 8 (pages 8 - 9) of the first ACD response. Similar reductions in hazard ratios for each CV event and the composite outcome were demonstrated in icosapent ethyl treated patients, which were sustained over the study period for each event, suggesting that the composite outcome was a representative metric for assessing CV risk and did not mask outlying hazard ratios in individual CV outcomes. The ERG was concerned that the hazard ratio for CV death and death from any cause were larger than that for the composite 5-point MACE however, it is important to note that the outcome of death was modelled separately to the other events, to ensure transparency of survival throughout the company model. Furthermore, a cross-validation model has been developed using individual CV outcomes instead of the composite 5-point MACE. The cross-validation model resulted in very similar clinical and economic outcomes to the model produced by the company, demonstrating that the use of the composite outcome does not mask the effect on individual CV outcomes and therefore does not introduce uncertainty in the model. Hence, using the composite 5-point MACE as an outcome in the company model is appropriate.	3.12.
8	Company	Amarin	**There is no evidence to support a treatment waning effect in patients receiving icosapent ethyl** Due to the lack of evidence to suggest that icosapent ethyl is associated with treatment waning in patients who discontinue treatment, it is reasonable to	The committee considered it implausible that the treatment effect would not reduce at any point after treatment discontinuation. It concluded it was reasonable to accept the scenario in which people stopping icosapent ethyl would

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			assume no treatment waning should be applied in the base case. This position was supported by a UK clinical expert, who commented, in response to the technical engagement, that "the company's assumption of no waning was likely reasonable". Treatment waning is already accounted for in the model as all patients who were treated with icosapent ethyl in the REDUCE-IT trial were modelled regardless of whether they discontinued treatment or not, so inclusion of an additional treatment waning effect is likely to underestimate the drug's clinical efficacy. Findings from REDUCE-IT summarised in section 10 (pages 13 – 14) of the first ACD response also showed sustained efficacy in patients who discontinued icosapent ethyl treatment compared to those who discontinued placebo. In section 3.15 of the ACD, it was noted that: "*It recognised that in NICE's appraisal of alirocumab, the company had assumed 100% treatment continuation and compliance over the entire time horizon. The committee noted that this assumption likely would not be appropriate in this appraisal because a significant proportion of people discontinued treatment by the end of follow-up in REDUCE-IT"*. It is important to note that the follow-up periods in the randomised controlled trials of the NICE approved PCSK9 inhibitors and bempedoic acid were a lot shorter at the time of the appraisals (median follow-up of 78 weeks for alirocumab and 52 weeks for bempedoic acid) than in the REDUCE-IT trial (maximum follow-up of 6.2 years). Therefore, it is expected that more patients would discontinue in the REDUCE-IT trial compared to these other trials, due to the longer follow-up duration. Furthermore, inclisiran and bempedoic acid were approved by NICE despite the committee concluding that there is uncertainty in the evidence informing the long-term treatment effect.[12,28] Furthermore, in section 3.15 of the ACD, the NICE clinical expert commented that given the absence of long-term data, it is difficult to determine the appropriateness of a treatment waning effect assumption. However, the expert noted that related treatments for CVD, such as statins, have long-term effects. The expert commented that the company's assumption of no treatment waning was likely reasonable.	lose treatment effect after 10 years. See FAD section 3.13.

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			The company therefore believes that assumptions of complete continuation and no treatment waning effect should be considered for this appraisal, as this is the assumption that has been used for other therapies in this area. Furthermore, there is no evidence to suggest that a treatment waning effect should be applied to patients taking icosapent ethyl, and it would be inappropriate to assume arbitrary waning timepoints to inform decision making.	
9	Company	Amarin	**Discrepancies between the original and updated cross-validations** In section 3.17 of the ACD, it was noted that: *"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"* To further clarify, the discrepancies found in the original cross-validation provided and those at the technical engagement stage was due to the proportion of patients having events being compared using different denominators. In the cross-validation model, the number of survivors at different points in time was used as a denominator while in the company's model, the number of patients at the start of the model (N=1,000) was used as a denominator. Therefore, the proportions produced were different between the two models. In the initial validation, we had not noticed the difference between the company model and the cross-validation model; for instance, the proportion of individuals event free and the proportion of individuals experiencing a first event in the cross-validation model did not sum to 100%, while in the company model they did. Once noticed, Amarin clarified the situation with the owner of the cross-validation model and then requested the denominator to be changed so that the proportions could be appropriately compared. Following this correction, the outcomes produced were similar between the two models.	Thank you for the clarification.
10	Company	Amarin	**Revised economic base case**	Because of the high level of uncertainty in

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			The committee has previously suggested that an acceptable incremental cost-effectiveness ratio (ICER) for decision making in this appraisal would be £20,000 per QALY gained, due to perceived uncertainty within the company submission. Therefore, it is important to note that applying further assumptions in the economic analysis to test uncertainty (such as applying a reduction in treatment effect and treatment waning) would likely be double counting uncertainty. As discussed in comment 5 of this response, the evidence on the theoretical effect of changes to biomarkers in the placebo arm of the REDUCE-IT trial clearly point to a hypothetical effect on the relative benefit of icosapent ethyl of between 0.3 to 3%. Hence, the company is proposing the midpoint of a 1.5% relative reduction in treatment effect, for the purpose of decision making in this appraisal. It should be noted that the ERG also did not recommend any reduction in treatment effect within their base case assumptions. Additionally, as discussed in comment 8 of this response, there is no evidence base to support the application of any treatment waning effect for patients discontinuing icosapent ethyl, and using arbitrary waning timepoints is not appropriate for decision making. Other treatments in this area have gained NICE approval assuming complete continuation and no treatment effect waning, which should also be applied for this appraisal. Amarin's priority is to ensure patients with the highest unmet need can access icosapent ethyl. When we consider the social impact and the impact on the wider determinants of health of the 5-point MACE endpoint, stroke is the one that impacts patients' lives the most post survival because of the disability it can leave the patient with. The scale and impact of stroke is enormous and growing – if we do nothing, the cost of stroke to the health and care system is estimated to rise from £26bn to between £61bn and £91bn by 2035. Importantly, 90% of all strokes are preventable, and by working together, we can lead the way in both reducing strokes and improving outcomes for patients.[29] The REDUCE-IT trial has demonstrated a reduction in the number of patients who go on to experience a fatal or non-fatal stroke. Therefore, icosapent ethyl is a much-needed therapy for reducing the risk of CV events	the clinical and economic evidence, the committee agreed that an acceptable ICER would be towards the lower end of the range normally considered a cost-effective use of NHS resources. See FAD section 3.15.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>such as strokes in patients with hypertriglyceridemia, a population in which there are currently no alternative treatment options available.

For these reasons, Amarin have considered the perceived uncertainties raised by the committee and have revised the company base case in the economic analysis.

The base case has been revised to capture the most conservative assumptions, detailed below, that should be considered for decision making:
• No treatment waning
• Maximum 1.5% relative reduction in treatment effect
• Updated list price of £[redacted]

With the assumptions applied above, the revised company base case results in an ICER of £20,000 (presented in Table 1 below).</td><td></td></tr>
<tr><td>11</td><td>Company</td><td>Amarin</td><td>Revised base case results

Table 1: Revised base case results (No treatment waning + 1.5% relative reduction in treatment effect, with a list price of £[redacted])
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incr. costs (£)</th><th>Incr. LYG</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Placebo</td><td>[redacted]</td><td>11.227</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Icosapent ethyl</td><td>[redacted]</td><td>11.587</td><td>[redacted]</td><td>[redacted]</td><td>0.359</td><td>[redacted]</td><td>20,000</td></tr>
</table>
Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years.

Table 2: Previous base case (No treatment waning + 0% relative reduction in treatment effect, with a list price of £[redacted])
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incr. costs (£)</th><th>Incr. LYG</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Placebo</td><td>[redacted]</td><td>11.20</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table></td><td>The committee's most plausible ICERs were between £21,750 and £24,821 per QALY gained. See FAD section 3.15. Therefore, it recommended icosapent ethyl for routine use.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			<table><tr><td></td><td></td><td>1</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Icosapent ethyl</td><td>[redacted]</td><td>11.587</td><td>[redacted]</td><td>[redacted]</td><td>0.385</td><td>[redacted]</td><td>19,848</td></tr></table>Abbreviations: ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years.	
12	Consultee	HEART UK	• Has all of the relevant evidence been taken into account? Mineral oil used in the placebo arm is an important issue and NICE should assess this. However, we feel the impact of this and 0.18 mmol/L increase in LDL-C in the placebo arm is overestimated. It is likely that Mineral oil interfered with statin absorption leading to 0.18 mmol/L increase in LDL-C in the placebo arm, this accounts for only ~4% (in statin clinical trials 1 mmol/L reduction corresponded to 22%% RRR) of the benefit leaving 20% RRR. The remaining 20% RRR is likely related to an increase in EPA level and other effects of EPA.	Thank you for your comment. Considering the company's analyses and the conclusion of the European Medicines Agency, the committee concluded that it would be appropriate to consider scenarios estimating a reduction in treatment effect from 1.5% to 3%, to account for the potential negative effect of the mineral oil placebo. See FAD section 3.9.
13	Consultee	HEART UK	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? There is a definite unmet need that can be addressed by making Vascepa available for NHS patients. We feel cost effectiveness can be improved if the company provides the drug at a discounted rate to NHS patients. The cost effectiveness should take into consideration an 18-20% RRR rather the 25% reported in the trials. This is to account for a possible effect of Mineral oil on statin absorption and the reflection of this on LDL-C level. Our opinion is in line with the FDA Assessment of the effect of mineral oil.	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
14	Consultee	HEART UK	• Are the recommendations a sound and suitable basis for guidance to the NHS? It is extremely disappointing this has not been accepted. CVD remains the biggest killer and there is very much an unmet need in this group of patients. Unresolved uncertainties in the interpretation of the evidence will leave secondary prevention patients who have controlled LDL-C at increased risk of recurrent events due to high absolute risk and persistent hypertriglyceridaemia without access to a potentially lifesaving novel therapy. There are no other	Thank you for your comments. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			therapeutics available for this patient group, their cardiovascular disease will continue to progress and these patients need access to this medicine in order to effectively manage their condition.	
15	Public	Web comment 1	• Has all of the relevant evidence been taken into account? No. I was disappointed to see that the committee has given a negative opinion in view of the issue with regards to the potential negative effects of mineral oil when used as placebo. A very good systematic review clearly demonstrated that this is not the case (European Heart Journal Supplements (2020) 22 (Supplement J), J34–J48). I am also not sure where the 14% estimation for the reduction of the efficacy of the medication came from. Is there any robust evidence for this figure? • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? As above • Are the recommendations sound and a suitable basis for guidance to the NHS? No, there is a very large unmet need for complementary lipid lowering therapies and this decision is obstructing the introduction of an agent that could help protect many patients from CV events. • 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? No	Thank you for your comment. Considering the company's analyses and the conclusion of the European Medicines Agency, the committee concluded that it would be appropriate to consider scenarios estimating a reduction in treatment effect from 1.5% to 3%, to account for the potential negative effect of the mineral oil placebo. See FAD section 3.9. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
16	Public	Web comment 2	• Has all of the relevant evidence been taken into account? Yes	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following

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			• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes • Are the recommendations sound and a suitable basis for guidance to the NHS? Yes • 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? Nil • Appraisal consultation comments I feel there is an unmet need for the management of triglycerides which can lead to increased risk of CVD. I feel triglycerides should be included when taking into account cardiovascular risk. I believe the evidence from clinical trial is robust and shows significant risk reduction in both CVD risk and mortality. The objection of mineral oil in the placebo I feel has little effect on the results.	the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
17	Public	Web comment 3	• Appraisal consultation comments I believe despite intensive LDL reduction, a significant CV risk remains for many patients. It has long been accepted that elevated triglyceride levels are also a marker of CV risk but without any substantiative evidence to demonstrate a risk benefit with current treatments eg Niacin/Fibrates. I believe	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD

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			elevated triglyceride levels could be underpinning the underlying CV risk still present in patients with optimal LDL control. It seems that Vazkepa as demonstrated in the REDUCE-IT Trial addresses the above risk across a broad population of relevant patients.	section 1.
18	Public	Web comment 4	• Appraisal consultation comments As a community pharmacist, I am frequently faced with patients concerned about their high cholesterol and LDL levels which despite optimal medications, lifestyle changes and concordance with medication remains a big clinical issue. So their cardiovascular protection is a still a big concern to them and me. Many of these patients, throughout my years as a pharmacist in the same community, have continued to have Heart attacks and strokes. Therefore in my opinion, Vazkepa and the evidence from the REDUCE IT clinical trial suggests that there is now another option which looks to be efficacious and more importantly, safe to support the patient group that I mentioned previously.	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
19	Public	Web comment 5	• Appraisal consultation comments This medication is going to be very helpful to the group of patients with residual cardiovascular risk, despite optimal treatment with statins. These patients almost certainly will have elevated triglycerides and there is no evidence based treatment options yet. I feel that the outcomes from the REDUCE- IT trial are strongly supporting the use of Vazkepa.	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
20	Public	Web comment 6	• Has all of the relevant evidence been taken into account? There is an unmet need. This product has a place because it addresses residual risks that are missed when only LDL reduction is the focus of our Patient Caring. I envisage a need for this to be added onto the latest and most novel LDL lowering drug therapies too. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			It actually seems more cost effective than NICE has considered. With new DES publication, and achieving better CVD outcomes beyond LDL, Icosapent Ethyl has a place, if not a strong position for consideration. • Are the recommendations sound and a suitable basis for guidance to the NHS? NICE should allow a TA for this product, Icosapent Ethyl. I would like to select CVD Patients, indeed Diabetics too, on a statin, with an additional CVD risk criteria, to be prescribed this new drug with robust data and, indeed, very significant NNTs. • 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? I have no problem, nor lack confidence in the outcomes of this drug, including a full rejection of negativity towards 'mineral oil' and would like that debate to end because the FDA had no problem with 'mineral oil' and there is nothing that alarms me in the EMA documentation either.	
21	Public	Web comment 7	• Has all of the relevant evidence been taken into account? Yes I have read all the evidence so far in the document and studies/ trials. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes all the evidence suggest that clinical & cost effectiveness have been taken into consideration effectively. • Are the recommendations sound and a suitable basis for guidance to the NHS?	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			Absolutely as we need more drugs like EPA to protect the high risk patients as many CVS targets are likely to be missed due to the pandemic and current pressure on the NHS. I say this from my experience of running the only Cardio Metabolic clinic in the NHS where I see many of these high risk patients. • 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? It works across the board in all patient groups. The latest evidence from WHO, called Pulse Survey suggests that up to 70% targets in NCDs globally are going to be missed over next 5 years due to the pandemic. Hence, drugs like EPA will play a very important role in post pandemic era for years to come.	
22	Public	Web comment 8	• Has all of the relevant evidence been taken into account? If the documentation around 'mineral oil' had been considered then surely the NICE TA would already be in place. The FDA documentation that I have considered is found here: https://www.fda.gov/media/132477/download The Summary: exploratory analysis indicates that the effect of LDL-C values on time to the primary endpoint is numerically small and unlikely to change the overall conclusion of the treatment benefit to be had with Icosapent Ethyl. Largest LDL-C differential per FDA analysis would translate to a maximal 3.1% of the observed 25% RRR. The prior reported benefits EPA consistent with REDUCE-IT were that of JELIS with a -19% RRR reported and did not include	Thank you for your comment. Considering the company's analyses and the conclusion of the European Medicines Agency, the committee concluded that it would be appropriate to consider scenarios estimating a reduction in treatment effect from 1.5% to 3%, to account for the potential negative effect of the mineral oil placebo. See FAD section 3.9. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			a placebo in that trial! The QALY should not be impacted by mineral oil inclusion and the RRR results should stay closer to the reported REDUCE-IT trial in real world use. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. It looks like it is cost-effective! I have calculated the savings that should result in reduction of non-elected admissions. These have not been analysed properly. I also think there is a place for biomarkers that see triglycerides reduced and the need for high EPA. Icosapent Ethyl does not have 'DHA' in it which seems to 'invert' the desired outcomes which are achieved successfully in REDUCE-IT. I believe that adding Icosapent Ethyl to Standard of Care (statin plus ezetimibe) is simpler than adding in PCSK9i's or even the Incliseran agenda of NHS England (Inclisiran does not have safety outcome data yet is not simple to prescribe and administer and will not report until at least 2027!). Icosapent Ethyl looks cost effective and simple to prescribe. Please make it available. • Are the recommendations sound and a suitable basis for guidance to the NHS? If NICE is going to recommend Icosapent Ethyl, my answer is yes. The biggest problem we have is the delay in getting this TA published because I have patients that would benefit from this today. Why are we delaying their care? They do not want more 'LDL reductions and are asking for other options. I want the option pf Icosapent Ethyl made available based upon the scientific evidence of the robust trial REDUCE-IT. Thank you for the opportunity of commenting. • 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	

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			maternity? Make Icosapent Ethyl available as soon as possible. I believe there are some revolutionary ideas around how we can use this technology to achieve better outcomes in Cardiovascular Disease Patient Care here in the United Kingdom, using NICE Guidance to give the confidence and reputation. Thank you for the opportunity to comment.	
23	Public	Web comment 9	• Are the recommendations sound and a suitable basis for guidance to the NHS? As a consultant in Cardiology, I believe that patients are in need of a further option of treatment beyond just LDL C control. I have reviewed NICE documentation and also the REDUCE IT trial for icosapent ethyl and believe that these significant reductions in MACE seen would be of benefit to these patients and it should be recommended	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
24	Public	Web comment 10	• Appraisal consultation comments Despite optimal LDL reduction we see increased CV risk in diabetes patients with raised TGs, and Vazkepa data / REDUCE-IT trial demonstrates that Vaskepa addresses the unmet need and improves CV outcomes	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
25	Public	Web comment 11	• Appraisal consultation comments There is a clear clinical need for Icosapent ethyl given the need to address raised TG levels in those with CV disease.	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
26	Public	Web comment 12	• Has all of the relevant evidence been taken into account? Mineral oil used in the placebo arm is an important issue. This was assessed by FDS and we feel NICE should also assess this in a fair and evidence based way. In statin RCT meta-analyses reducing one mmol LDL-C with statins	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Considering the company's analyses and the conclusion of the European Medicines

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			corresponded to 22% RRR. We feel the impact of 0.18 mmol/L increase in LDL-C in the placebo arm, likely to be due to mineral oil interference with statin absorption, is overestimated. It is likely that Mineral oil interfered with statin absorption leading to 0.18 mmol/L increase in LDL-C in the placebo arm, this accounts for only ~4% of the benefit, leaving 20% RRR that is achieved by Icosapent ethyl. The mechanism by which icosapent ethyl reduced cardiovascular risk is not fully understood and was not related to reduction TG level. However, the following should be taken in consideration: 1. Many other medication (like SGLT2 inhibitors) reduce ASCVD risk and improve heart failure outcomes but the exact mechanist is still debated. 2. Other studies outcome like JELIS study, which is consistent with REDUCE IT study 3. TG has a wide biological variability and this may account, at least in part, for the lack of correlation between outcomes and TG level. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? There is a definite unmet need that can be addressed by making Vascepa available for NHS patients. We feel cost effectiveness can be improved if the company and NICE work together to agree an arrangement to improve cost effectiveness. Otherwise, we in specialist lipid clinics and our patients would be very disappointed to see atherosclerotic vascular disease of certain patient groups (with high TG and ASVCD) increase and unable to access the medication that can address this. • Are the recommendations sound and a suitable basis for guidance to the NHS? I would extremely disappointing this has not been accepted as there are patients who need this treatment with no other alternatives, we see these patients regularly with progression of atherosclerotic vascular disease despite	Agency, the committee concluded that it would be appropriate to consider scenarios estimating a reduction in treatment effect from 1.5% to 3%, to account for the potential negative effect of the mineral oil placebo. See FAD section 3.9. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			controlling LDL-C and other traditional risk factors but TG remains high. • 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? It would be extremely disappointing if this drug is not approved and patients with high/very high ASCVD risk (who tend to be those with type 2 diabetes, obesity and genetically determined high TG) would be disadvantaged and I feel also unlawfully discriminated.	
27	Public	Web comment 13	• Has all of the relevant evidence been taken into account? Yes, the Reduce-It trial is a well conducted study. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes • Are the recommendations sound and a suitable basis for guidance to the NHS? Yes • 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? No	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
28	Public	Web comment 14	• Has all of the relevant evidence been taken into account?	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an

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			I don't think NICE has looked at how significant REDUCE-IT is, and how relevant for the unmet needs in the UK. I want this option to look into residual risk reductions. Very interesting. Friend and Colleagues in USA are using this based on the Trial and getting encouraging outcomes. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I think NICE is missing how cost effective this is. When it reaches Primary Care, there are positive implications for outcomes. They have new outcomes frameworks and new DES this Spring (imminent). We need technologies that help address it. I see an answer in Icosapent Ethyl. • Are the recommendations sound and a suitable basis for guidance to the NHS? I think the 'mineral oil' argument is false and unscientific. NEJM published REDUCE-IT, for goodness sake! The US Body, FDA chose the Placebo, not the drug company. ERG looks very positive. Make it available please. • 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? I think the data is relevant fir the UK. Over 8,000 Patients across 11 countries. 4.9 years and minimal patient loss. This is strong, significant evidence. The EMA do not have a problem with it. Outcome data sits better with me than being asked to give an injection that hasn't got outcome data. Let's get back to strong safety data, not 'political agendas' set by non-medics. Thanks.	option for reducing the risk of cardiovascular events in adults. See FAD section 1.
29	Public	Web comment 15	• Has all of the relevant evidence been taken into account? Yes	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes • Are the recommendations sound and a suitable basis for guidance to the NHS? On the basis of available evidence, this therapy meets an unmet need for reducing residual CVD risk in patients, especially among people with type 2 diabetes. High trig is a feature of insulin resistance, which is an important marker of cardiovascular diseases. Clinical trial data showed very impressive NNT to reduce CV event among patients with elevated Trig, but normal LDL- who would otherwise not receive further cardiovascular protective lipid lowering agents. • 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? No	
30	Public	Web comment 16	• Are the recommendations sound and a suitable basis for guidance to the NHS? I have been able to review the consultation documentation of icosapent ethyl and reviewed the REDUCE-IT outcomes. From this data it shows that patients have significant cardiovascular risks despite standard factors being controlled. Based on current evidence I believe another option for treatment would be helpful in optimizing patient outcomes	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Icosapent ethyl would be beneficial in improving outcomes as per trial data Mineral oil placebo is unlikely to significantly affect outcome of data as per FDA and EMA modelling	
31	Public	Web comment 17	• Has all of the relevant evidence been taken into account? Yes • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes • Are the recommendations sound and a suitable basis for guidance to the NHS? Yes. However, it is notable that icosapent ethyl has demonstrated a significant reduction in cardiovascular events within high-risk groups. The consultation casts doubt on this reduction, and its generalisability to the NHS in England. It is unclear how important these doubts were in the decision not to recommend icosapent ethyl. Were they as significant a factor as the concerns over cost-effectiveness? Assuming that the REDUCE-IT methodology is judged to be sound, it seems likely that there would be a place for icosapent ethyl within the NHS, but that further consideration needs to be given to the most appropriate patient group and the cost of the drug. • 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?	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			No	
32	Public	Web comment 18	• Are the recommendations sound and a suitable basis for guidance to the NHS? Having reviewed all the medical data to date including REDUCE-IT trial evidence, the recommendations appear sound for NHS guidance. The drug appears to be well tolerated with minimal side-effects and the potential for CV risk reduction is immense particularly in diabetic patients. As a cardiologist, the data appears exciting & compelling for use and approval as soon as possible. There is already good 5 year data available.	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
33	Public	Web comment 19	• Has all of the relevant evidence been taken into account? Yes • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes • Are the recommendations sound and a suitable basis for guidance to the NHS? Yes they are clear and concise • 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? No	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
34	Public	Web comment 20	• Has all of the relevant evidence been taken into account? I do feel that the evidence submitted is relevant ad does show some key data regarding the efficacy and safety of the therapy with regards to providing	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1).

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			additional therapy in order to reduce CV risk – especially in the secondary prevention group • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes, I do believe so, but further analysis of the numbers within the England population to quantify the need would enable us to use this therapy in the appropriate cohort who are high risk. But overall do feel the clinical and cost effectiveness are justified • Are the recommendations sound and a suitable basis for guidance to the NHS? Yes, I do think there is a need for additional therapies such as this to improve outcomes and reduce morbidity and mortality in this high risk group, especially when no other therapies appear to produce results similar to this drug. Agree the should be promoted alongside diet and lifestyle changes, but the reductions in MACE are significant enough to warrant NICE approval • 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? I do feel the question of mineral oil acting as a confounder is being used to deny much needed therapy to this high risk group and the FDA did not feel this was an issue to change the balance of the outcomes in the trials. In fact it was concluded to have minimal effect and this does not explain the 25%RRR achieved. Even if 3-5% max was attributed to the mineral oil – there is still a >20% RRR which justifies its clinical need	Considering the company's analyses and the conclusion of the European Medicines Agency, the committee concluded that it would be appropriate to consider scenarios estimating a reduction in treatment effect from 1.5% to 3%, to account for the potential negative effect of the mineral oil placebo. See FAD section 3.9. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
35	Public	Web comment 21	• Has all of the relevant evidence been taken into account?	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Icosapent Ethyl has been considered by Health Canada, US FDA to be used as an add-on maximally tolerated statin therapy in patients with elevated triglycerides with established CV disease or with diabetes plus 2 or more CV risk factors. Has NICE looked at the body of evidence which these bodies took into consideration when making their decision? • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No, it is hard to understand the clinical and cost effectiveness interpretations of the evidence evaluated. Cost comparator should also include the cost of surgical procedures which these patients would undergo once they have coronary events due to residual risk. • Are the recommendations sound and a suitable basis for guidance to the NHS? No, one should take into consideration the subpopulation where this drug has been able to make the difference as shown in EVAPORATE trial. EPA modulates atherosclerotic plaque features which would lead to higher overall atherosclerotic plaque stability. Here beneficial effects are enhanced when given in combination with a statin so the role is specific to treatment of residual CV risk inS hypertriglyceridaemic patients with well controlled LDL-c levels. NHS currently has no guidance for this group of patients • 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? This drug has shown increased benefit in South Asian population who have also been noticed to have secondary coronary events despite being treated with high dose statins. This subsection also has higher prevalence of Diabetes as well.	option for reducing the risk of cardiovascular events in adults. See FAD section 1.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
36	Public	Web comment 22	• Are the recommendations sound and a suitable basis for guidance to the NHS? Having reviewed the consultation document and the trial data I feel it appropriate to make comment. I believe that the trial data does demonstrate patients experience significant cardiovascular risk even when standard factors such as LDL-cholesterol have been controlled and I believe another method of treatment would be extremely useful to have for these patients. From the REDUCE-IT trial, significant reduction in MACE have been shown with an acceptable tolerability and I believe this would of clinical benefit as a a useful addition to existing treatment for our cardiology patient with significant underlying coronary disease to help reduce further cardiovascular risk.	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
37	Public	Web comment 23	• Are the recommendations sound and a suitable basis for guidance to the NHS? As an acute physician I spend a large amount of my clinical time looking after patients with cardiovascular disease. The vast majority of these individuals are already established on statin therapy to reduce the incidence of further cardiovascular events. Despite being on traditional agents, a large proportion of such patients will go on to suffer further cardiac events, which can result in debilitating chronic conditions that can adversely affect an individual's lifestyle or worse still result in death. This in itself highlights the importance of doing more, and as such it is important other strategies / agents are used to further reduce and mitigate this risk. Upon review of the literature there appears to be promising relative reductions in major adverse cardiovascular events with the use of icosapent ethyl. For me the key to such treatment options is tolerability and the agent has shown a favourable tolerability profile. The agent has shown impressive reductions in ischaemic events and this has been demonstrated in multiple trials, and appears to be independent of any effects from the mineral oil. Whilst I understand the issues raised with use of mineral oil and potential interference with statin absorption, I do not feel this to	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			be significant enough to explain the relative risk reductions observed. My own view as to the positive efficacy of this drug is echoed by the FDA and EMA. I do feel that NICE should take into consideration multicentre randomised controlled trial data as the conclusions presented in this are much more credible and robust than those seen in the observational study's where the efficacy of icosapent ethyl is questioned.	
38	Public	Web comment 24	• Appraisal consultation comments There is an unmet need for elevated triglycerides levels in relation to CV risk reduction. I believe TG should be included in patient lipid testing as a routine test. I believe the evidence in reduce it trial is robust with strong CV end points being met showing statistically significant reduction in CV risk. In my opinion mineral oil in the placebo arm cannot be a factor effecting efficacy due to FDA recommending mineral oil being used in the control arm.	Thank you for your comment. The committee agreed that people with raised triglycerides would welcome a treatment option (see FAD section 3.1). Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
39	Public	Web comment 25	• Appraisal consultation comments Cardiovascular risk reduction remains a major public health issue and an important component of which is optimising lipid management. Whilst statins are by and large effective from this point of view a residual risk remains (Particularly in individuals with Diabetes). Being of South Asian origin myself I am aware that my personal lipid profile has a component of hypertriglycaremia. Having reviewed the trial evidence published in NEJM paper on Icosapent ethyl in addition to statin, I strongly recommend its widespread use to reduce the residual cardiovascular risk.	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.
40	Public	Web comment 26	• Has all of the relevant evidence been taken into account? Yes • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No.	Thank you for your comment. The committee considered that there was some uncertainty in the trial results because REDUCE-IT may not fully represent NHS clinical practice (see FAD section 3.6). Considering the company's analyses and the conclusion of the European Medicines Agency, the committee concluded that it would be appropriate to consider scenarios

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			With respect to clinical effectiveness, the decision to reject the clinical benefit demonstrated in the REDUCE-IT trial because the trial included a mineral oil-treated comparator group in not scientifically justified. As the committee acknowledges, the scientific literature demonstrates inconsistent effects of mineral oil treatment on lipid parameters and inflammatory markers. Many studies of cardiovascular risk reduction demonstrate a modest increase in LDL-cholesterol levels in statin-treated arms. The clinical scenario studied in REDUCE-IT, in which patients were enrolled with well-treated LDL cholesterol levels but elevated triglycerides, is common in clinical practice. It is inappropriate scientifically for NICE to largely base its decision not to recommend Icosapent ethyl in this group on its interpretation of what is essentially a questionable influence of mineral oil treatment in the comparator group. The committee's decision that Icosapent ethyl should not be supported because the participants recruited to the REDUCE-IT trial differed from the population covered by NHS England is also not clinically justified. If this argument were to be followed, many clinical trials in the cardiovascular research field would be dismissed. The logical conclusion of the committee's comments here is that only trials conducted in England can reasonably be used to inform NICE decisions. This is obviously not the case - there are many examples in which medications have been recommended by NICE when the characteristics of the trial population or comparator treatments differed substantially from usual practice in England. Pertinent examples are in the field of anti-platelet therapy, in which the dose of aspirin administered in England differs from that studied in clinical trials; and geographical variation in clinical response was noted in the PLATO trial of ticagrelor. Reassuringly, there was no significant interaction according to ethnicity in REDUCE-IT which provides support that the findings are applicable to the population of England. Whilst is acknowledged that 'optimal' therapy may evolve during the conduct of any clinical trial, that cannot be used as a cogent argument to dismiss findings of clinical benefit. There are many examples of drugs being recommended by NICE on the basis of clinical studies carried out before contemporary treatments have been widely deployed (examples are the NICE recommendations for SGLT2 inhibitors in heart failure with reduced ejection	estimating a reduction in treatment effect from 1.5% to 3%, to account for the potential negative effect of the mineral oil placebo. See FAD section 3.9. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			fraction, when deployment of treatment with angiotensin-neprolysin inhibitors in the clinical trials could be argued to be low in relation to optimal contemporary practice). The inclusion of the comment from the clinical advisor that "standard care in the NHS for diabetes includes SGLT2 inhibitors but it is uncertain how many people in REDUCE-IT had these treatments" is disingenuous, when NICE guidance on management of diabetes in adults (NG28) was only updated in February 2022 to recommend the positioning of SGLT2 inhibitors for cardiovascular risk reduction in type 2 diabetes. • Are the recommendations sound and a suitable basis for guidance to the NHS? The recommendations are not sound for the reasons indicated in relation to the summaries of clinical effectiveness. • 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? No	
41	Public	Web comment 27	• Has all of the relevant evidence been taken into account? REDUCE-IT is very strong and robust ‘safety outcomes data.’ Gives confidence. • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Looks like there is a place for this. NICE needs to see what I can see: I can see it fitting into the 2022/23 DES and Outcomes Framework, especially	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			considering our tasks to treat Ambulatory Care Sensitive Cases in 2022 and beyond. Icosapent Ethyl has a strong place and looks cost effective in reducing residual risks. It is making me rethink how I read Triglycerides as a bio-marker and something to act upon. • Are the recommendations sound and a suitable basis for guidance to the NHS? I would like to have the choice to prescribe this and look forward to a NICE TA for guidance. • 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? Please make it available for Secondary Care and Primary Care.	
42	Public	Web comment 28	• Are the recommendations sound and a suitable basis for guidance to the NHS? I have reviewed the consultation document and looked at the trial data. I feel i am able to make comments. I believe that patients have significant cardiovascular risk despite standard factors such LDL-C have been controlled. Based on our current evidence I believe another modality for treatment would be useful and needed for these patients. From the REDUCE-IT trial it has shown significant reduction in MACE alongside an acceptable tolerability profile. I sincerely believe that icosapent ethyl would be a very much needed and useful addition.	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults. See FAD section 1.

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			Concerning suggestions that treatments effects are uncertain because of the mineral oil placebo I feel that this not born out of the data. My view is aligned and supported by the modelling by the FDA and EMA.	
43	Public	Web comment 29	• Appraisal consultation comments Currently, Icosapent ethyl is licensed for use in patients with Tg > 1.7mmol/L while on statins in the setting of prior cardiovascular disease or have diabetes and one other CVS risk factor. Using the above parameters, the number of eligible patients in UK will be significantly high. What I would suggest NICE consider is a narrower eligibility using non-HDL cholesterol as an additional criteria rather than purely Triglycerides only. Important to note that non-HDL-C (non-fasting sample of Total cholesterol - HDL cholesterol) is more reflective of atherogenicity in persons with elevated triglycerides. The constellation of increased triglycerides, reduced HDL-C, increased small dense LDL particles, and increased remnant cholesterol levels (primarily VLDL), is known as atherogenic type dyslipidaemia. Instead of just using the cut off for Tg > 1.7mmol/L, we should target the highest risk group of patients and I would propose a Tg > 4.5mmol/L with a non-HDL cholesterol > 5.7mmol/L in the setting where the patient is already on maximum tolerated statins.	Thank you for your comment. Following the second consultation, the committee recommended icosapent ethyl as an option for reducing the risk of cardiovascular events in adults with raised triglycerides (1.7 mmol/litre or above). See FAD section 1.

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 19 April 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 welcome the opportunity to comment on this Appraisal Consultation Document (ACD), and kindly ask the committee to reconsider its recommendation published in the ACD in light of the additional clarifying evidence provided. Cardiovascular disease (CVD) is the leading cause of death in the UK.[1] Despite traditional risk factor control in patients with established CVD, it is estimated that more than a third of patients will experience a major adverse cardiovascular (CV) event within 5-7 years.[2] There are 6.7 million people living with CVD in England and Wales and the annual cost to the National Health Service (NHS) is more than £9 billion per year. The coronavirus pandemic (COVID-19) has exacerbated CVD healthcare burden, resulting in an estimated 50,000-100,000 excess CVD deaths in England during the pandemic.[3] The NHS Long Term Plan regards CVD as '*the single biggest area where the NHS can save lives over the next 10 years*'. The plan explicitly aims to prevent 150,000 heart

attacks, strokes and vascular dementia cases by 2029, in order to improve CV mortality. It is estimated that a further 12,000 avoidable heart attacks and strokes will occur by 2025, if missed opportunities for treatment initiation due to the coronavirus pandemic are not addressed. This highlights the urgent need for a treatment that can reduce the risk of CV events and reduce CV mortality rates for years to come.

Currently there are no specific treatments available to lower CV risk in adult statin-treated patients with established CVD, elevated serum triglycerides (1.69 to 5.63 mmol/L) and controlled LDL-C.

The REDUCE-IT trial demonstrated that icosapent ethyl significantly reduces major adverse CV events in adult statin-treated patients with established CVD and elevated triglycerides (1.69 to 5.63 mmol/L).[4] On this basis, the European Society of Cardiology (ESC) guidelines recommend to consider '*icosapent ethyl (2x2g/day) in combination with statins'* for the treatment of hypertriglyceridemia in high CV risk patients.[5]

Amarin have sought to address the concerns raised by the committee, which will reduce the uncertainty in making a recommendation. This includes:

- Input from nine UK clinical experts from a recent medical advisory board indicating that the data from the REDUCE-IT trial would be generalisable to the UK population. This compliments the previously supplied observational studies of established CVD patients by Steen 2017, Lawler 2020 and Ferrières 2020, showing broadly similar baseline characteristics between the trial and Steen cohorts as well as similar CV risk between the trial and the Western European populations.[6–8]

- Three additional within-trial analyses conducted by the company quantifying the hypothetical effect of elevations in hs-CRP and LDL-C on the placebo arm of the REDUCE-IT trial, which further demonstrate that the maximum theoretical effect of placebo on the relative benefit of icosapent ethyl is approximately 1.5%.

- Validation of the clinical outcomes estimated by the economic model by three UK clinical experts. A cross-validation was also undertaken with an external published, peer reviewed Markov model, to compare the clinical and economic outputs with the company model.[9]

- Additional evidence to justify why no treatment waning should be applied to patients discontinuing icosapent ethyl.

Amarin also would like to highlight our concern to the committee that 'uncertainty' in this appraisal is taken into account twice in defining NICE's preferred incremental cost-effectiveness ratio (ICER) – once to justify lowering the willingness to pay threshold from £30,000 to £20,000 per QALY (a *de facto* up to 33% reduction in the commonly used acceptable ICER threshold set by NICE), and a second time in suggesting a treatment waning effect and in reducing the relative efficacy of icosapent ethyl vs. placebo. This is considered by the company as a disproportionate application of uncertainty adjustment tools by NICE.

Attempting to take into account for a proportionate application of any residual uncertainty remaining after the additional evidence provided, Amarin have submitted a

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

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	revised company base case. Changes to the company base case are as follows: application of no treatment waning, a maximum hypothetical effect of placebo of 1.5% relative reduction in treatment effect, and a revision of the list price of icosapent ethyl from £173.00 per pack of 120 capsules, to £[redacted] A detailed summary of all the uncertainties raised by the committee and how these have been addressed can be found in sections 1 – 10. All new evidence has been provided in the appendix at the end of this document.
2	**The population in REDUCE-IT is generalisable to the NHS in England** In section 3.6 of the ACD, it was noted that: "*The population in REDUCE-IT may not be generalisable to the NHS in England*". The company has already provided the committee with multiple lines of evidence from populations analogous to the UK population including France, Canada and the UK, indicating similarities in baseline characteristics and levels of residual CV risk.[6–8] In addition, an advisory board conducted by Amarin on 24th March 2022, including nine UK clinical experts from the specialties of cardiology, diabetology, chemical pathology and general practice, supported the view that the data from REDUCE-IT would be generalisable to the UK population. Clinical experts indicated that there is no reason to believe that the results of REDUCE-IT would not be applicable to UK clinical practice. In section 3.7 of the ACD, it was noted that: "*The committee concluded that the current management of cardiovascular disease and diabetes is not fully reflected in REDUCE-IT, so the generalisability of the trial results is uncertain*". The company wishes to reiterate that usage of agents such as SGLT2 inhibitors and GLP-1 agonists was consistent with the time-period over which the REDUCE-IT trial was enrolling patients ([redacted]% and [redacted]%, respectively). Furthermore, patients who are not diabetic would not necessarily be eligible for treatment with these agents, and no statistically significant interaction for the efficacy of icosapent ethyl was observed in the REDUCE-IT trial when comparing patients with and without diabetes at baseline (HR 0.77 vs. 0.73, P_{int} = 0.56).[4] The use of PCSK9 inhibitors is not relevant to this appraisal as patients eligible for icosapent ethyl have LDL-C levels below 2.6 mmol/L as per the trial inclusion criteria. Patients in England and Wales are only eligible for PCSK9 inhibitors (alirocumab, evolocumab) when LDL-C levels are above 2.6 mmol/L (NICE TAs 393, 394, 733).[10–12]
3	**Icosapent ethyl's mechanism of action** In section 3.8 of the ACD, it was noted that: "*The committee concluded that the mechanism of action for icosapent ethyl is not fully understood, which adds uncertainty to the trial's results*".

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	The committee's position that a lack of certainty about the mechanism of action of icosapent ethyl creates uncertainty in the results of the REDUCE-IT trial is not clinically relevant to the interpretation of the overall outcomes measurement. During a recent medical advisory board, UK clinical experts remarked that a well-understood mechanism of action is not a requirement for clinical use, and many drugs available to prescribe have unknown mechanisms of action and have been highly beneficial for patients. For example, metformin, SGLT2 inhibitors and GLP1 agonists. In addition, preclinical studies have identified several modes of action that support a role for EPA, the active drug of icosapent ethyl, in beneficially altering the development, progression, and stabilisation of atherosclerotic plaque. These include 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.[13] The atheroprotective mechanisms exerted by EPA are further discussed by Mason PR *et al.,* and the committee is referred to this publication.[14] It is worth noting that additional clinical studies of icosapent ethyl have confirmed effects on reducing coronary atherosclerotic plaque volume.[15,16] Ongoing research by different groups will further explain the pleiotropic effect of icosapent ethyl in the upcoming years. Section 3.8 of the ACD also states: *"…that the reduction in cardiovascular risk observed in REDUCE-IT was larger than what would be expected from a reduction in triglycerides alone."* The company wishes to point out this is entirely consistent with what is known about icosapent ethyl. Post-hoc analyses of the effects of variations in baseline or achieved triglyceride levels on the benefit of icosapent ethyl vs. placebo in the REDUCE-IT trial have not demonstrated any interactions (Figure 2 and Figure 3). The European Medicines Agency (EMA) also concluded in its assessment of icosapent ethyl that *"TG reduction appears to provide only a minor contribution to the reduction in risk of cardiovascular events with icosapent ethyl*."[17]
4	**Mineral oil placebo in REDUCE-IT and difference in results between the REDUCE-IT and STRENGTH trials** In section 3.9 of the ACD, a professional group and the NHS England clinical adviser have commented that: "…*mineral oil may not be a true neutral oil and may have increased the risk of cardiovascular events in the placebo group. This would exaggerate the observed difference in cardiovascular events between the icosapent ethyl and placebo groups."* The company rejects this conclusion on the grounds that there is no evidence to suggest that mineral oil is not a true neutral oil, or that it increases the risk of CV events. The observed changes in biological parameters in the REDUCE-IT trial are in-line with placebo changes observed in 79% of CV outcomes trials conducted between 2003-2019, that did not employ mineral oil as placebo.[18] This includes the placebo arms of other trials involving other compounds recently appraised by NICE such as alirocumab

(Figure 4). More plausible explanations for these changes include regression to the mean effects after study inclusion and natural history of the disease, as noted by the regulatory authorities.

The safety of mineral oil is generally inferred from a long history of use with limited adverse effects and from use as placebo in other clinical studies. A systematic review of the literature including 80 studies that utilised mineral oil as placebo did not demonstrate directionally consistent effects on parameters such as triglycerides or LDL-C, including in the subgroup of studies on patients with established CVD or diabetes.[18]

The placebo in the REDUCE-IT trial was composed of pharmaceutical-grade, light-mineral oil, comprising straight-chain n-alkanes 15-26 carbon atoms in length.[18] This was manufactured under Good Manufacturing Practice conditions identical to other investigational medicinal products used in clinical trials. It was selected as the most appropriate placebo after discussion with regulatory authorities. Structurally, pharmaceutical-grade mineral oils (straight-chain n-alkanes) are not dissimilar to commonly consumed saturated and unsaturated fatty acids, including the polyunsaturated, monounsaturated and saturated fatty acids present in corn oil, e.g. stearic and linoleic acid.[19]

In section 3.9 of the ACD, 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 company rejects this conclusion of similarity on the grounds that different active compounds were investigated in the REDUCE-IT and STRENGTH trials. Regulatory authorities have made clear statements distinguishing icosapent ethyl, a pure EPA compound, from other mixed omega-3 preparations containing EPA and DHA. The Committee for Medicinal Products for Human use (CHMP) considers icosapent ethyl to be *"a new active substance as it differs significantly in properties with regard to efficacy from known mixture of 'omega-3-acid ethyl esters 90' contained in medicinal product(s) previously authorised within the European Union".*[17] Therefore, it is unreasonable for the committee to conclude similar results from these CV outcomes trials should be expected.

Numerous CV outcomes trials examining the effects of mixed omega-3 (EPA / DHA) compounds have failed to show any CV benefit.[20–22] In contrast, two large CV outcomes trials of icosapent ethyl have shown statistically significant benefits in reducing CV events over a median five years of follow-up; one of which, the JELIS trial, was not performed against a mineral oil placebo.[4,23]

Several lines of evidence indicate that EPA and DHA have distinct tissue distribution patterns, cell membrane locations and distinct physiologic functions as a consequence of differing carbon chain lengths (22 vs. 20) and number of double bonds (6 vs. 5). Additionally, laboratory studies suggest when EPA and DHA are combined in equal amounts, the membrane effects of both are attenuated, suggesting EPA & DHA have counter-regulatory actions.[24] A meta-analysis of randomised placebo-controlled trials of

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	monotherapy with EPA, DHA, or EPA vs. DHA has also demonstrated different effects on lipid parameters including LDL-C, HDL-C and triglycerides, which have established clinically relevant relationships with CV outcomes.[25]
5	**It is not appropriate to consider scenarios for an estimated reduction in treatment effect from 3% to 10%** In section 3.9 of the ACD, it is stated that: *"…the committee concluded it would be appropriate to consider scenarios estimating a reduction in treatment effect from 3% to 10%, based on the discussion in the EPAR. The committee considered the scenario using around 7% in its preferred analysis because it was near the middle of the range and aligned with Doi et al."* The company rejects this conclusion for several reasons. Firstly, the committee was incorrect to state that the conclusion of the CHMP in the EPAR was 10%. The Risk-Benefit Conclusion of the CHMP taken from the EPAR is reproduced *verbatim* below: *"Taking into consideration that such effects cannot be independently summed up, in a worst-case scenario attributing all of these effects to mineral oil, a putative negative impact of mineral oil on MACE should be below 10%. However, this is still an overestimation.* *Regression to the mean effects and the natural course of the disease may considerably have contributed to the increase in LDL-C and apoB. Furthermore, the scenario does not consider that the increase in HDL-C could be beneficial. Analyses taking physicochemical properties of drugs, efficacy and bleeding patterns into account did not indicate a major impact of mineral oil on absorption of statins, antiplatelet drugs and anticoagulants. However, e.g. the analyses of bleeding patterns were hampered by the fact that Vazkepa itself increases the risk of bleeding. Based on analyses as provided by the applicant, a putative negative effect of mineral oil should not account for more than 0.3 – 3% of MACE events."*[17] Therefore, it should be clear to the committee that the conclusion of the CHMP is that the maximum negative hypothetical effect could be 3%. This determination is actually based on an independent covariate adjusted Cox regression analysis performed by the FDA, not by the company as stated incorrectly in the EPAR, which the company subsequently provided to the EMA. This independent analysis is described at length in the FDA Briefing Document Endocrinologic and Metabolic Drugs Advisory Committee Meeting November 14, 2019, and the company requests the committee refer to this document when making its conclusions.[26] In deference to the committee, the analysis conducted by the FDA has been independently replicated here by the company using the REDUCE-IT trial dataset. Importantly, whilst several of the biological parameters that changed in the placebo arm of the REDUCE-IT trial are correlated with CV risk, their effects are not mutually exclusive and therefore cannot be simply summed. For example, changes in LDL-C are accounted for in considering changes in non-HDL-C or apoB.

Therefore, when considering the effects of these parameters on CV risk, it is only reliable to estimate the additive effects of changes in one or two of the related lipid parameters (e.g., LDL-C, and apoB) and hs-CRP, which may reasonably be considered to independently effect CV outcomes. This is the same approach taken by Doi *et al.* It is also important to account for the theoretical positive effects of the observed 5.7% increase in HDL-C in the placebo arm of the REDUCE-IT trial, and to adjust for other variables in the *within-trial* dataset known to affect CV outcomes such as age and diabetes status etc. using *within-trial* data on covariates, which could not be done by Doi *et al*.

The results of the company's replication of the FDA Cox regression model, examining the effects of hs-CRP and LDL-C as covariates on the relative benefit of icosapent ethyl, both from the perspective of the maximum absolute level at year 1 for LDL-C and year 2 for hs-CRP, and the change from baseline values, including a broader range of LDL-C analysis methods than was done by the FDA, are shown in Figure 5.

[redacted]27

The company has also conducted a new propensity score matched approach to the Cox regression analysis, accounting for the overlapping effects of LDL-C, hs-CRP and apoB.

[redacted]27

The company also wishes to provide the following additional evidence to support the maximum hypothetical 3% negative effect of biological parameter changes in the placebo arm. Patients in the REDUCE-IT trial underwent measurement of serum active drug concentration (EPA) annually during the trial. At the end of year 1, EPA levels increased by 393% in the icosapent ethyl arm and decreased by 13% in the placebo arm compared to baseline. An exposure response analysis was performed, including all available data points, comparing achieved EPA level with primary CV outcomes.

The relationship between CV outcomes and on-treatment serum EPA was evaluated as a spline-smoothed function of on-treatment serum EPA using a Cox proportional hazard model with serum EPA as a continuous covariate, stratified by randomisation factors (CV risk stratum, geographic region, and baseline ezetimibe use), and adjusted for other potentially confounding factors including statin adherence, age, sex, baseline non-HDL-C and baseline hs-CRP.
Figure 6 shows the relationship between achieved serum EPA drug level and the relative risk of the primary composite CV outcome for all patients enrolled in the REDUCE-IT trial, including placebo.

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	[redacted] The analysis conducted by Doi *et al*., used by the committee to inform the 7% reduction in efficacy, was derived from a non-UK, Danish observational cohort. It is not a good proxy for the expected efficacy of icosapent ethyl in the UK population. Furthermore, the demographics of the Doi 2021 cohort purportedly mimicking the REDUCE-IT cohort have significant differences in terms of age, proportion of females, proportion of Caucasians, percentage diabetic, and median triglycerides (Figure 1).[17] Even with multivariate adjustment, the committee must acknowledge there will be a high degree of unmeasured confounding in the analysis that makes it a poor surrogate for the efficacy of icosapent ethyl when compared to placebo. As previously pointed out to the committee by both the company and the ERG, the Doi 2021 analysis has a number of other limitations including lack of data on statin usage over time and lack of repeated measurement of biomarkers, that make it unsuitable to inform this appraisal. It is also important to note that using a simulation from a Danish observational study to inform the base case analysis is not appropriate, considering randomised controlled trial evidence exists in the form of REDUCE-IT. In summary, based on multiple lines of evidence, supported by independent analyses by regulatory authorities, weighed against the obvious limitations of a single, retrospectively designed, observational study by Doi *et al*., the company believes the committee should accept the scientifically based determination that the hypothetical negative effect of biological parameter changes in the placebo arm of REDUCE-IT should be the midpoint of 0.3-3% of the relative benefit of icosapent ethyl; around 1.5%, which is in-line with the company's new base case.
6	**A cross-validation model demonstrated the appropriateness of the company's model structure, showing that concerns raised in the ACD have minimal impact on clinical and economic outcomes** 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 (e.g., unable to skip or return to a previous state). The company model uses the time from randomisation to a first, second or third plus event, to ensure there are no issues surrounding crossover of the first, second or 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. A state-transition model in TreeAge, developed and adapted to a UK perspective by the MedStar group (published in the JAMA Network Open, from a US healthcare perspective),[9] was 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

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	data from REDUCE-IT for the in-trial period, then using a microsimulation model and data from published literature for the lifetime analysis. Despite using a different model structure and assumptions, the company's model produces very similar results to the cross-validation model, which removes uncertainty surrounding the modelling approach adopted and therefore demonstrates that the company's economic model is a suitable method for predicting clinical and economic outcomes for icosapent ethyl versus standard of care. Assumptions included in the cross-validation model satisfy the concerns raised by the ERG and NICE committee within section 3.12 of the ACD regarding the company model. The cross-validation model includes the following assumptions: 1. A traditional Markov modelling approach (validating the company's partSA modelling approach and addressing concerns regarding the assumption of independence of first, second and third plus MACE events). 2. The 5-point MACE outcome was modelled by each of the individual components (validating the company's assumption of modelling using the composite 5-point MACE endpoint). 3. A 6-month cycle length (validating the company's use of a one-day cycle length). 4. Published literature for predicting survival beyond the in-trial period (validating long term survival applied within the company's model). When comparing the two models, clinical outcomes remain consistent regardless of modelling assumptions used. For example, the proportion of individuals experiencing events and survival rates at set time points were similar between the company and cross-validation models across all assumptions tested. This demonstrates that the choice of model structure adopted by the company is appropriate, as it simulates results in line with what you would expect from a more conventional state-transition approach within this disease area. In section 3.12 of the ACD, it was noted that: *"The model appeared to overestimate mortality in both the placebo and icosapent ethyl groups in the 5-year comparison".* Three UK clinical experts consulted believed that the survival estimates produced from the model were similar to what they would expect to observe in UK clinical practice. They believed the remaining discrepancies between the overall mortality in the REDUCE-IT trial and the company model were likely attributed to the controlled environment of a clinical trial setting. The UK clinical experts consulted specifically 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. Finally, in section 3.17 of the ACD, it was noted that: *"There were still uncertainties about the company's model structure (see section 3.12)."*

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	The company would like to clarify that the purpose of the comparison with the cross-validation model was not to further support the company base case ICER or inputs used within the model, but it was in fact to support the robustness of using an alternative modelling approach with the same set of data, and what the impact of this would be for decision making. The comparison with the cross-validation model has demonstrated that the partSA approach used in the company model is appropriate for predicting clinical and economic outcomes within this disease area.
7	**A similar trend in results is observed for each individual component of the 5-point MACE** In section 3.13 of the ACD, it was noted that: "*Using the composite 5-point MACE outcome in the model increases uncertainty*". 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 were provided for the secondary prevention cohort in response to the first ACD. Hazard ratios for CV death, nonfatal MI, nonfatal stroke, coronary revascularisation, and unstable angina in the REDUCE-IT trial were presented in section 8 (pages 8 - 9) of the first ACD response. Similar reductions in hazard ratios for each CV event and the composite outcome were demonstrated in icosapent ethyl treated patients, which were sustained over the study period for each event, suggesting that the composite outcome was a representative metric for assessing CV risk and did not mask outlying hazard ratios in individual CV outcomes. The ERG was concerned that the hazard ratio for CV death and death from any cause were larger than that for the composite 5-point MACE however, it is important to note that the outcome of death was modelled separately to the other events, to ensure transparency of survival throughout the company model. Furthermore, a cross-validation model has been developed using individual CV outcomes instead of the composite 5-point MACE. The cross-validation model resulted in very similar clinical and economic outcomes to the model produced by the company, demonstrating that the use of the composite outcome does not mask the effect on individual CV outcomes and therefore does not introduce uncertainty in the model. Hence, using the composite 5-point MACE as an outcome in the company model is appropriate.
8	**There is no evidence to support a treatment waning effect in patients receiving icosapent ethyl** Due to the lack of evidence to suggest that icosapent ethyl is associated with treatment waning in patients who discontinue treatment, it is reasonable to assume no treatment waning should be applied in the base case. This position was supported by a UK clinical expert, who commented, in response to the technical engagement, that "the company's assumption of no waning was likely reasonable". Treatment waning is already accounted for in the model as all patients who were treated with icosapent ethyl in the REDUCE-IT trial were modelled regardless of whether they discontinued treatment or not, so inclusion of an additional treatment waning effect is likely to underestimate the drug's clinical efficacy. Findings from REDUCE-IT summarised in section 10 (pages 13

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	– 14) of the first ACD response also showed sustained efficacy in patients who discontinued icosapent ethyl treatment compared to those who discontinued placebo. In section 3.15 of the ACD, it was noted that: "*It recognised that in NICE's appraisal of alirocumab, the company had assumed 100% treatment continuation and compliance over the entire time horizon. The committee noted that this assumption likely would not be appropriate in this appraisal because a significant proportion of people discontinued treatment by the end of follow-up in REDUCE-IT"*. It is important to note that the follow-up periods in the randomised controlled trials of the NICE approved PCSK9 inhibitors and bempedoic acid were a lot shorter at the time of the appraisals (median follow-up of 78 weeks for alirocumab and 52 weeks for bempedoic acid) than in the REDUCE-IT trial (maximum follow-up of 6.2 years). Therefore, it is expected that more patients would discontinue in the REDUCE-IT trial compared to these other trials, due to the longer follow-up duration. Furthermore, inclisiran and bempedoic acid were approved by NICE despite the committee concluding that there is uncertainty in the evidence informing the long-term treatment effect.[12,28] Furthermore, in section 3.15 of the ACD, the NICE clinical expert commented that given the absence of long-term data, it is difficult to determine the appropriateness of a treatment waning effect assumption. However, the expert noted that related treatments for CVD, such as statins, have long-term effects. The expert commented that the company's assumption of no treatment waning was likely reasonable. The company therefore believes that assumptions of complete continuation and no treatment waning effect should be considered for this appraisal, as this is the assumption that has been used for other therapies in this area. Furthermore, there is no evidence to suggest that a treatment waning effect should be applied to patients taking icosapent ethyl, and it would be inappropriate to assume arbitrary waning timepoints to inform decision making.
9	**Discrepancies between the original and updated cross-validations** In section 3.17 of the ACD, it was noted that: *"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"* To further clarify, the discrepancies found in the original cross-validation provided and those at the technical engagement stage was due to the proportion of patients having events being compared using different denominators. In the cross-validation model, the number of survivors at different points in time was used as a denominator while in the company's model, the number of patients at the start of the model (N=1,000) was used as a denominator. Therefore, the proportions produced were different between the two models.

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	In the initial validation, we had not noticed the difference between the company model and the cross-validation model; for instance, the proportion of individuals event free and the proportion of individuals experiencing a first event in the cross-validation model did not sum to 100%, while in the company model they did. Once noticed, Amarin clarified the situation with the owner of the cross-validation model and then requested the denominator to be changed so that the proportions could be appropriately compared. Following this correction, the outcomes produced were similar between the two models.
10	**Revised economic base case** The committee has previously suggested that an acceptable incremental cost-effectiveness ratio (ICER) for decision making in this appraisal would be £20,000 per QALY gained, due to perceived uncertainty within the company submission. Therefore, it is important to note that applying further assumptions in the economic analysis to test uncertainty (such as applying a reduction in treatment effect and treatment waning) would likely be double counting uncertainty. As discussed in comment 5 of this response, the evidence on the theoretical effect of changes to biomarkers in the placebo arm of the REDUCE-IT trial clearly point to a hypothetical effect on the relative benefit of icosapent ethyl of between 0.3 to 3%. Hence, the company is proposing the midpoint of a 1.5% relative reduction in treatment effect, for the purpose of decision making in this appraisal. It should be noted that the ERG also did not recommend any reduction in treatment effect within their base case assumptions. Additionally, as discussed in comment 8 of this response, there is no evidence base to support the application of any treatment waning effect for patients discontinuing icosapent ethyl, and using arbitrary waning timepoints is not appropriate for decision making. Other treatments in this area have gained NICE approval assuming complete continuation and no treatment effect waning, which should also be applied for this appraisal. Amarin's priority is to ensure patients with the highest unmet need can access icosapent ethyl. When we consider the social impact and the impact on the wider determinants of health of the 5-point MACE endpoint, stroke is the one that impacts patients' lives the most post survival because of the disability it can leave the patient with. The scale and impact of stroke is enormous and growing – if we do nothing, the cost of stroke to the health and care system is estimated to rise from £26bn to between £61bn and £91bn by 2035. Importantly, 90% of all strokes are preventable, and by working together, we can lead the way in both reducing strokes and improving outcomes for patients.[29] The REDUCE-IT trial has demonstrated a reduction in the number of patients who go on to experience a fatal or non-fatal stroke. Therefore, icosapent ethyl is a much-needed therapy for reducing the risk of CV events such as strokes in patients with hypertriglyceridemia, a population in which there are currently no alternative treatment options available. For these reasons, Amarin have considered the perceived uncertainties raised by the committee and have revised the company base case in the economic analysis.

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	The base case has been revised to capture the most conservative assumptions, detailed below, that should be considered for decision making: • No treatment waning • Maximum 1.5% relative reduction in treatment effect • Updated list price of £[redacted] With the assumptions applied above, the revised company base case results in an ICER of £20,000 (presented in Table 1 below).

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Revised base case results

Table 1: Revised base case results *(No treatment waning + 1.5% relative reduction in treatment effect, with a list price of £[redacted])*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Placebo	[redacted]	11.227	[redacted]	-	-	-	-
Icosapent ethyl	[redacted]	11.587	[redacted]	[redacted]	0.359	[redacted]	20,000

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

Table 2: Previous base case *(No treatment waning + 0% relative reduction in treatment effect, with a list price of £[redacted])*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Placebo	[redacted]	11.201	[redacted]	-	-	-	-
Icosapent ethyl	[redacted]	11.587	[redacted]	[redacted]	0.385	[redacted]	19,848

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

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New evidence

The population in REDUCE-IT is generalisable to the NHS in England

Figure 1: Baseline demographics from REDUCE-IT and the Danish observational cohort from Doi *et al.*[30]

	REDUCE-IT[1,a]	CGPS mimicking REDUCE-IT
No.	8179	5684
Age (years)	64 (57–69)	70 (63–76)
Women	2357 (28)	2109 (37)
Body mass index (kg/m2)	31 (28–35)	28 (25–31)
Whites	7379 (90)	5684 (100)
ASCVD	5785 (71)	4061 (71)
Diabetes	4787 (59)	2405 (42)
Hypertension	NA[d]	4944 (88)
Statins	8179 (100)	5684 (100)
Median follow-up (years)	4.9	4.9
Plasma triglycerides		
mmol/L	2.5 (2.0–3.1)	1.6 (1.1–2.3)
mg/dL	217 (177–272)	140 (97–203)
LDL cholesterol		
mmol/L	1.9 (1.6–2.3)	2.1 (1.7–2.6)
mg/dL	74 (62–88)	81 (66–101)
Non-HDL cholesterol		
mmol/L	3.1[e]	2.9 (2.4–3.5)
mg/dL	118[e]	111 (91–133)
Plasma apolipoprotein B (g/L)	0.82[e]	0.88 (0.72–1.07)
Plasma C-reactive protein (mg/L)	2.2 (1.1–4.5)	1.5 (1.0–2.7)
ASCVD during follow-up		
No.	1606[f]	852
Events/1000 person-years	40[f,g]	34

Abrevations: ASCVD – atherosclerotic cardiovascular diseases; CGPS – Copenhagen General Population Study; HDL – high-density lipoprotein; LDL – low-density lipoprotein; NA – not available; REDUCE-IT – Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; SD – standard deviation
Values are shown as median (interquartile range) or n (%), unless otherwise stated.
a: Values for REDUCE-IT represent those for the icosapent ethyl arm except for ASCVD; however, values were similar for the comparator mineral oil arm.
d: Prevalence of hypertension was not reported in REDUCE-IT.
e: Interquartile range was not reported in REDUCE-IT.
f: Numbers include events from both active and comparator oil arms in REDUCE-IT
g: Events per 1000 person-years in REDUCE-IT or STRENGTH were estimated by number of ASCVD events in both arms during follow-up divided by median follow-up in years multiplied with numbers of individuals.

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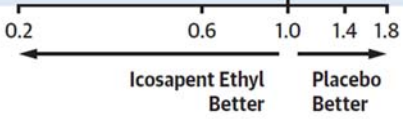
Icosapent ethyl's mechanism of action

Figure 2: Relative benefit of icosapent ethyl according to baseline triglyceride levels in the REDUCE-IT trial[31]

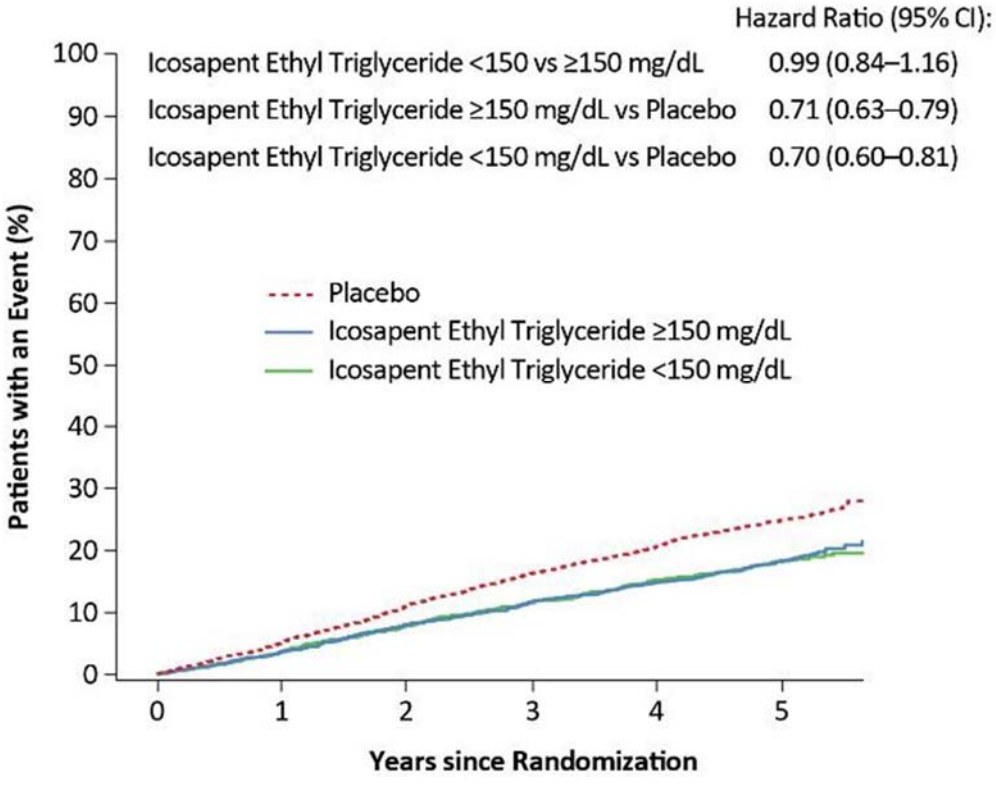
TIME TO FIRST EVENT – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	HR (95% CI)	P-Value
	n/N (%)	n/N (%)		
Primary Composite Endpoint (ITT)	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68-0.83)	< 0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dl	233/1378 (16.9)	291/1381 (21.1)	0.79 (0.66-0.94)	0.0069
>190 to ≤250 mg/dl	246/1370 (18.0)	283/1326 (21.3)	0.80 (0.68-0.95)	0.0121
>250 to ≤1401 mg/dl	226/1338 (16.9)	327/1382 (23.7)	0.68 (0.57-0.80)	< 0.0001



*P (interaction) = 0.33

Abbreviations: CI – confidence interval; HR – hazard ratio; ITT – intent to treat; RR – rate ratio
The primary composite endpoint event consists of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina.

Figure 3: Relative benefit (primary endpoint) of icosapent ethyl according to achieved triglyceride levels in the REDUCE-IT trial[31]



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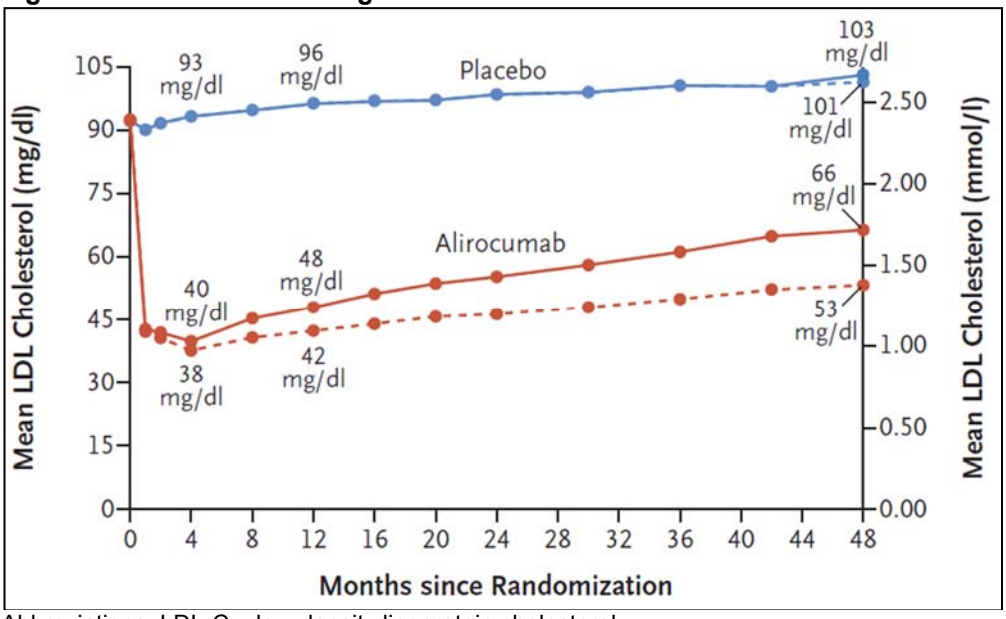
The primary composite endpoint event consists of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina.

Mineral oil placebo in REDUCE-IT and difference in results between the REDUCE-IT and STRENGTH trials

Figure 4: LDL-C levels during the ODYSSEY OUTCOMES trial[32]



Abbreviations: LDL-C – low-density lipoprotein cholesterol
Adapted from Schwartz, GG et al. N Eng J Med 2018;379:2097-107

It is not appropriate to consider scenarios for an estimated reduction in treatment effect from 3% to 10%

Figure 5: A Cox proportional hazards model with treatment as a factor, stratified by geographic region, CV risk category and use of ezetimibe with hs-CRP or LDL-C as continuous covariates[27]

[redacted]

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Abbreviations: AMR101 – icosapent ethyl; CV – cardiovascular; HDL-C – high-density lipoprotein cholesterol; hsCRP – High-sensitivity C-reactive protein; ITT – intention-to-treat; LDL-C – low-density lipoprotein cholesterol

Table 3: Propensity score matching results to quantify maximum potential placebo effect[27]

Matching biomarkers	Adjusted HR	Unadjusted HR	Delta in HR (Maximum potential placebo effect)
LDL-C Hopkins + hsCRP + ApoB	[redacted]	[redacted]	[redacted]
LDL-C Hopkins + hsCRP	[redacted]	[redacted]	[redacted]
LDL-C Hopkins	[redacted]	[redacted]	[redacted]
hsCRP	[redacted]	[redacted]	[redacted]
ApoB	[redacted]	[redacted]	[redacted]
LDL-C Derived + hsCRP + ApoB	[redacted]	[redacted]	[redacted]
LDL-C Derived + hsCRP	[redacted]	[redacted]	[redacted]
LDL-C Derived	[redacted]	[redacted]	[redacted]
hsCRP	[redacted]	[redacted]	[redacted]
ApoB	[redacted]	[redacted]	[redacted]

Abbreviations: ApoB – apolipoprotein B; HR – hazard ratio; hsCRP – high-sensitivity C-reactive protein; LDL-C – low-density lipoprotein cholesterol

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Figure 6: Spline-smoothed exposure response relationship between on-treatment serum EPA (ug/mL) and risk reduction in primary composite endpoint referencing to baseline EPA level (icosapent ethyl + placebo patients)[27]

Abbreviations: CI – confidence interval; EPA – eicosapentaenoic acid; HDL – high-density lipoprotein; hsCRP – high-sensitivity C-reactive protein; IPE – icosapent ethyl

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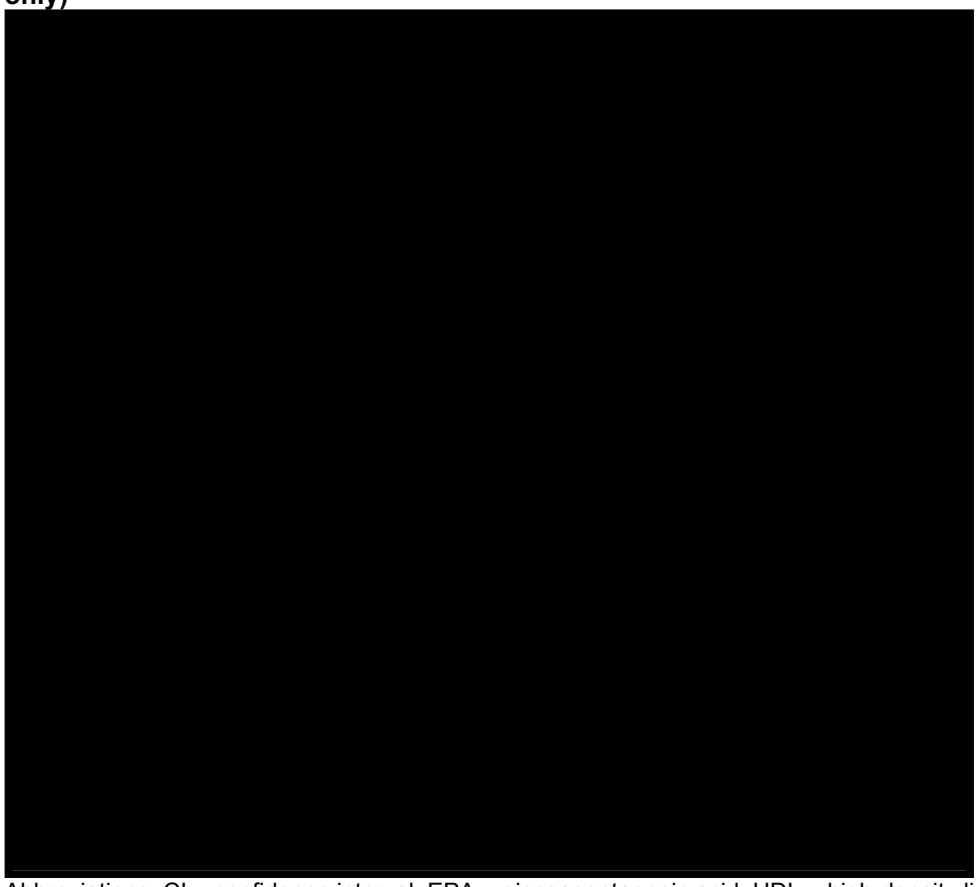
Figure 7: Spline-smoothed exposure response relationship between on-treatment serum EPA (ug/mL) and risk reduction in primary composite endpoint referencing to baseline EPA level (icosapent ethyl patients only)[27]



Abbreviations: CI – confidence interval; EPA – eicosapentaenoic acid; HDL – high-density lipoprotein; hsCRP – high-sensitivity C-reactive protein; IPE – icosapent ethyl

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Figure 8: Theoretical placebo effect - difference in HRs of the exposure-response curves between the whole population (icosapent ethyl + placebo patients) and the icosapent ethyl only patients[27]

Abbreviations: CI – confidence interval; EPA – eicosapentaenoic acid; HR – hazard ratio; hsCRP – high-sensitivity C-reactive protein; IPE – icosapent ethyl

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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 19 April 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

Please return to: **NICE DOCS**

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 19 April 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	• Has all of the relevant evidence been taken into account? Mineral oil used in the placebo arm is an important issue and NICE should assess this. However, we feel the impact of this and 0.18 mmol/L increase in LDL-C in the placebo arm is overestimated. It is likely that Mineral oil interfered with statin absorption leading to 0.18 mmol/L increase in LDL-C in the placebo arm, this accounts for only ~4% (in statin clinical trials 1 mmol/L reduction corresponded to 22%% RRR) of the benefit leaving 20% RRR. The remaining 20% RRR is likely related to an increase in EPA level and other effects of EPA.
2	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? There is a definite unmet need that can be addressed by making Vascepa available for NHS patients. We feel cost effectiveness can be improved if the company provides the drug at a discounted rate to NHS patients. The cost effectiveness should take into consideration an 18-20% RRR rather the 25% reported in the trials. This is to account for a possible effect of Mineral oil on statin absorption and the reflection of this on LDL-C level. Our opinion is in line with the FDA Assessment of the effect of mineral oil.
3	• Are the recommendations a sound and suitable basis for guidance to the NHS? It is extremely disappointing this has not been accepted. CVD remains the biggest killer and there is very much an unmet need in this group of patients. Unresolved uncertainties in the interpretation of the evidence will leave secondary prevention patients who have controlled LDL-C at increased risk of recurrent events due to high absolute risk and persistent hypertriglyceridaemia without access to a potentially lifesaving novel therapy. There are no other therapeutics available for this patient group, their cardiovascular disease will continue to progress and these patients need access to this medicine in order to effectively manage their condition.
4	
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

Please return to: **NICE DOCS**

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 19 April 2022**. Please submit via NICE Docs.

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 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.

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:

- Has all of the relevant evidence been taken into account?

No. I was disappointed to see that the committee has given a negative opinion in view of the issue with regards to the potential negative effects of mineral oil when used as placebo. A very good systematic review clearly demonstrated that this is not the case (European Heart Journal Supplements (2020) 22 (Supplement J), J34–J48). I am also not sure where the 14% estimation for the reduction of the efficacy of the medication came from. Is there any robust evidence for this figure?

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

As above

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, there is a very large unmet need for complementary lipid lowering therapies and this decision is obstructing the introduction of an agent that could help protect many patients from CV events.

- 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?

No

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes

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

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

- 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?

Nil

- Appraisal consultation comments

I feel there is an unmet need for the management of triglycerides which can lead to increased risk of CVD. I feel triglycerides should be included when taking into account cardiovascular risk.

I believe the evidence from clinical trial is robust and shows significant risk reduction in both CVD risk and mortality.

The objection of mineral oil in the placebo I feel has little effect on the results.

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

Comments on the ACD:

- Appraisal consultation comments

I believe despite intensive LDL reduction, a significant CV risk remains for many patients. It has long been accepted that elevated triglyceride levels are also a marker of CV risk but without any substantiative evidence to demonstrate a risk benefit with current treatments eg Niacin/Fibrates. I believe elevated triglyceride levels could be underpinning the underlying CV risk still present in patients with optimal LDL control.

It seems that Vazkepa as demonstrated in the REDUCE-IT Trial addresses the above risk across a broad population of relevant patients.

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

Comments on the ACD:

- Appraisal consultation comments

As a community pharmacist, I am frequently faced with patients concerned about their high cholesterol and LDL levels which despite optimal medications, lifestyle changes and concordance with medication remains a big clinical issue. So their cardiovascular protection is a still a big concern to them and me. Many of these patients, throughout my years as a pharmacist in the same community, have continued to have Heart attacks and strokes. Therefore in my opinion, Vazkepa and the evidence from the REDUCE IT clinical trial suggests that there is now another option which looks to be efficacious and more importantly, safe to support the patient group that I mentioned previously.

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

Comments on the ACD:

- Appraisal consultation comments

This medication is going to be very helpful to the group of patients with residual cardiovascular risk, despite optimal treatment with statins.

These patients almost certainly will have elevated triglycerides and there is no evidence based treatment options yet.

I feel that the outcomes from the REDUCE- IT trial are strongly supporting the use of Vazkepa.

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

There is an unmet need. This product has a place because it addresses residual risks that are missed when only LDL reduction is the focus of our Patient Caring. I envisage a need for this to be added onto the latest and most novel LDL lowering drug therapies too.

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

It actually seems more cost effective than NICE has considered. With new DES publication, and achieving better CVD outcomes beyond LDL, Icosapent Ethyl has a place, if not a strong position for consideration.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

NICE should allow a TA for this product, Icosapent Ethyl. I would like to select CVD Patients, indeed Diabetics too, on a statin, with an additional CVD risk criteria, to be prescribed this new drug with robust data and, indeed, very significant NNTs.

- 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?

I have no problem, nor lack confidence in the outcomes of this drug, including a full rejection of negativity towards 'mineral oil' and would like that debate to end because the FDA had no problem with 'mineral oil' and there is nothing that alarms me in the EMA documentation either.

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes I have read all the evidence so far in the document and studies/ trials.

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

Yes all the evidence suggest that clinical & cost effectiveness have been taken into consideration effectively.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Absolutely as we need more drugs like EPA to protect the high risk patients as many CVS targets are likely to be missed due to the pandemic and current pressure on the NHS.

I say this from my experience of running the only Cardio Metabolic clinic in the NHS where I see many of these high risk patients.

- 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?

It works across the board in all patient groups.

The latest evidence from WHO, called Pulse Survey suggests that up to 70% targets in NCDs globally are going to be missed over next 5 years due to the pandemic. Hence, drugs like EPA will play a very important role in post pandemic era for years to come.

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

If the documentation around 'mineral oil' had been considered then surely the NICE TA would already be in place.

The FDA documentation that I have considered is found here:

https://www.fda.gov/media/132477/download

The Summary: exploratory analysis indicates that the effect of LDL-C values on time to the primary endpoint is numerically small and unlikely to change the overall conclusion of the treatment benefit to be had with Icosapent Ethyl.

Largest LDL-C differential per FDA analysis would translate to a maximal 3.1% of the observed 25% RRR. The prior reported benefits EPA consistent with REDUCE-IT were that of JELIS with a -19% RRR reported and did not include a placebo in that trial! The QALY should not be impacted by mineral oil inclusion and the RRR results should stay closer to the reported REDUCE-IT trial in real world use.

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

No. It looks like it is cost-effective! I have calculated the savings that should result in reduction of non-elected admissions. These have not been analysed properly. I also think there is a place for biomarkers that see triglycerides reduced and the need for high EPA. Icosapent Ethyl does not have 'DHA' in it which seems to 'invert' the desired outcomes which are achieved successfully in REDUCE-IT. I believe that adding Icosapent Ethyl to Standard of Care (statin plus ezetimibe) is simpler than adding in PCSK9i's or even the Incliseran agenda of NHS England (incliseran does not have safety outcome data yet is not simple to prescribe and administer and will not report until at least 2027!).

Icosapent Ethyl looks cost effective and simple to prescribe. Please make it available.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

If NICE is going to recommend Icosapent Ethyl, my answer is yes. The biggest problem we have is the delay in getting this TA published because I have patients that would benefit from this today. Why are we delaying their care? They do not want more 'LDL reductions and are asking for other options. I want the option pf Icosapent Ethyl made available based upon the scientific evidence of the robust trial REDUCE-IT. Thank you for the opportunity of commenting.

- 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?

Make Icosapent Ethyl available as soon as possible. I believe there are some revolutionary ideas around how we can use this technology to achieve better outcomes in Cardiovascular Disease Patient Care here in the United Kingdom, using NICE Guidance to give the confidence and reputation. Thank you for the opportunity to comment.

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

Comments on the ACD:

- Are the recommendations sound and a suitable basis for guidance to the NHS?

As a consultant in Cardiology, I believe that patients are in need of a further option of treatment beyond just LDL C control. I have reviewed NICE documentation and also the REDUCE IT trial for icosapent ethyl and believe that these significant reductions in MACE seen would be of benefit to these patients and it should be recommended

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

Comments on the ACD:

- Appraisal consultation comments

Despite optimal LDL reduction we see increased CV risk in diabetes patients with raised TGs, and Vazkepa data / REDUCE-IT trial demonstrates that Vaskepa addresses the unmet need and improves CV outcomes

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

Comments on the ACD:

- Appraisal consultation comments

There is a clear clinical need for Icosapent ethyl given the need to address raised TG levels in those with CV disease.

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Mineral oil used in the placebo arm is an important issue. This was assessed by FDS and we feel NICE should also assess this in a fair and evidence based way. In statin RCT meta-analyses reducing one mmol LDL-C with statins corresponded to 22% RRR. We feel the impact of 0.18 mmol/L increase in LDL-C in the placebo arm, likely to be due to mineral oil interference with statin absorption, is overestimated.

It is likely that Mineral oil interfered with statin absorption leading to 0.18 mmol/L increase in LDL-C in the placebo arm, this accounts for only ~4% of the benefit, leaving 20% RRR that is achieved by Icosapent ethyl.

The mechanism by which icosapent ethyl reduced cardiovascular risk is not fully understood and was not related to reduction TG level. However, the following should be taken in consideration:

1. Many other medication (like SGLT2 inhibitors) reduce ASCVD risk and improve heart failure outcomes but the exact mechanist is still debated.
2. Other studies outcome like JELIS study, which is consistent with REDUCE IT study
3. TG has a wide biological variability and this may account, at least in part, for the lack of correlation between outcomes and TG level.

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

There is a definite unmet need that can be addressed by making Vascepa available for NHS patients. We feel cost effectiveness can be improved if the company and NICE work together to agree an arrangement to improve cost effectiveness. Otherwise, we in specialist lipid clinics and our patients would be very disappointed to see atherosclerotic vascular disease of certain patient groups

(with high TG and ASVCD) increase and unable to access the medication that can address this.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I would extremely disappointing this has not been accepted as there are patients who need this treatment with no other alternatives, we see these patients regularly with progression of atherosclerotic vascular disease despite controlling LDL-C and other traditional risk factors but TG remains high.

- 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?

It would be extremely disappointing if this drug is not approved and patients with high/very high ASCVD risk (who tend to be those with type 2 diabetes, obesity and genetically determined high TG) would be disadvantaged and I feel also unlawfully discriminated.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Nottingham University Hospitals NHS Trust
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes, the Reduce-It trial is a well conducted study.

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

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

- 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?

No

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

I don't think NICE has looked at how significant REDUCE-IT is, and how relevant for the unmet needs in the UK. I want this option to look into residual risk reductions. Very interesting. Friend and Colleagues in USA are using this based on the Trial and getting encouraging outcomes.

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

I think NICE is missing how cost effective this is. When it reaches Primary Care, there are positive implications for outcomes. They have new outcomes frameworks and new DES this Spring (imminent). We need technologies that help address it. I see an answer in Icosapent Ethyl.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I think the 'mineral oil' argument is false and unscientific. NEJM published REDUCE-IT, for goodness sake! The US Body, FDA chose the Placebo, not the drug company. ERG looks very positive. Make it available please.

- 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?

I think the data is relevant fir the UK. Over 8,000 Patients across 11 countries. 4.9 years and minimal patient loss. This is strong, significant evidence. The EMA do not have a problem with it. Outcome data sits better with me than being asked to give an injection that hasn't got outcome data. Let's get back to strong safety data, not 'political agendas' set by non-medics. Thanks.

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes

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

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

On the basis of available evidence, this therapy meets an unmet need for reducing residual CVD risk in patients, especially among people with type 2 diabetes. High trig is a feature of insulin resistance, which is an important marker of cardiovascular diseases. Clinical trial data showed very impressive NNT to reduce CV event among patients with elevated Trig, but normal LDL- who would otherwise not receive further cardiovascular protective lipid lowering agents.

- 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?

No

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

Comments on the ACD:

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I have been able to review the consultation documentation of icosapent ethyl and reviewed the REDUCE-IT outcomes.

From this data it shows that patients have significant cardiovascular risks despite standard factors being controlled.

Based on current evidence I believe another option for treatment would be helpful in optimizing patient outcomes

Icosapent ethyl would be beneficial in improving outcomes as per trial data

Mineral oil placebo is unlikely to significantly affect outcome of data as per FDA and EMA modelling

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes

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

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes. However, it is notable that icosapent ethyl has demonstrated a significant reduction in cardiovascular events within high-risk groups. The consultation casts doubt on this reduction, and its generalisability to the NHS in England. It is unclear how important these doubts were in the decision not to recommend icosapent ethyl. Were they as significant a factor as the concerns over cost-effectiveness?

Assuming that the REDUCE-IT methodology is judged to be sound, it seems likely that there would be a place for icosapent ethyl within the NHS, but that further consideration needs to be given to the most appropriate patient group and the cost of the drug.

- 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?

No

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

Comments on the ACD:

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Having reviewed all the medical data to date including REDUCE-IT trial evidence, the recommendations appear sound for NHS guidance. The drug appears to be well tolerated with minimal side-effects and the potential for CV risk reduction is immense particularly in diabetic patients. As a cardiologist, the data appears

exciting & compelling for use and approval as soon as possible. There is already good 5 year data available.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

Yes

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

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes they are clear and concise

- 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?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

I do feel that the evidence submitted is relevant ad does show some key data regarding the efficacy and safety of the therapy with regards to providing additional therapy in order to reduce CV risk - especially in the secondary prevention group

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

Yes, I do believe so, but further analysis of the numbers within the England population to quantify the need would enable us to use this therapy in the appropriate cohort who are high risk. but overall do feel the clinical and cost effectiveness are justified

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes, I do think there is a need for additional therapies such as this to improve outcomes and reduce morbidity and mortality in this high risk group, especially when no other therapies appear to produce results similar to this drug.
Agree the should be promoted alongside diet and lifestyle changes, but the reductions in MACE are significant enough to warrant NICE approval

- 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?

I do feel the question of mineral oil acting as a confounder is being used to deny much needed therapy to this high risk group and the FDA did not feel this was an issue to change the balance of the outcomes in the trials. In fact it was concluded to have minimal effect and this does not explain the 25%RRR achieved. even if 3-5% max was attributed to the mineral oil - there is still a >20% RRR which justifies its clinical need

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Icosapent Ethyl has been considered by Health Canada, US FDA to be used as an add-on maximally tolerated statin therapy in patients with elevated triglycerides with established CV disease or with diabetes plus 2 or more CV risk factors. Has NICE looked at the body of evidence which these bodies took into consideration when making their decision?

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

No, it is hard to understand the clinical and cost effectiveness interpretations of the evidence evaluated. Cost comparator should also include the cost of surgical procedures which these patients would undergo once they have coronary events due to residual risk.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, one should take into consideration the subpopulation where this drug has been able to make the difference as shown in EVAPORATE trial. EPA modulates atherosclerotic plaque features which would lead to higher overall atherosclerotic plaque stability. Here beneficial effects are enhanced when given in combination

with a statin so the role is specific to treatment of residual CV risk inS hypertriglyceridaemic patients with well controlled LDL-c levels. NHS currently has no guidance for this group of patients

- 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?

This drug has shown increased benefit in South Asian population who have also been noticed to have secondary coronary events despite being treated with high dose statins. This subsection also has higher prevalence of Diabetes as well.

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

Comments on the ACD:

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Having reviewed the consultation document and the trial data I feel it appropriate to make comment. I believe that the trial data does demonstrate patients experience significant cardiovascular risk even when standard factors such as LDL-cholesterol have been controlled and I believe another method of treatment would be extremely useful to have for these patients. From the REDUCE-IT trial, significant reduction in MACE have been shown with an acceptable tolerability and I believe this would of clinical benefit as a a useful addition to existing treatment for our cardiology patient with significant underlying coronary disease to help reduce further cardiovascular risk.

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

Comments on the ACD:

- Are the recommendations sound and a suitable basis for guidance to the NHS?

As an acute physician I spend a large amount of my clinical time looking after patients with cardiovascular disease. The vast majority of these individuals are already established on statin therapy to reduce the incidence of further cardiovascular events.

Despite being on traditional agents, a large proportion of such patients will go on to suffer further cardiac events, which can result in debilitating chronic conditions that can adversely affect an individual’s lifestyle or worse still result in death. This in

itself highlights the importance of doing more, and as such it is important other strategies / agents are used to further reduce and mitigate this risk.

Upon review of the literature there appears to be promising relative reductions in major adverse cardiovascular events with the use of icosapent ethyl. For me the key to such treatment options is tolerability and the agent has shown a favourable tolerability profile.

The agent has shown impressive reductions in ischaemic events and this has been demonstrated in multiple trials, and appears to be independent of any effects from the mineral oil. Whilst I understand the issues raised with use of mineral oil and potential interference with statin absorption, I do not feel this to be significant enough to explain the relative risk reductions observed. My own view as to the positive efficacy of this drug is echoed by the FDA and EMA.

I do feel that NICE should take into consideration multicentre randomised controlled trial data as the conclusions presented in this are much more credible and robust than those seen in the observational study's where the efficacy of icosapent ethyl is questioned.

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

Comments on the ACD:

- Appraisal consultation comments

There is an unmet need for elevated triglycerides levels in relation to CV risk reduction.
I believe TG should be included in patient lipid testing as a routine test.
I believe the evidence in reduce it trial is robust with strong CV end points being met showing statistically significant reduction in CV risk.

In my opinion mineral oil in the placebo arm cannot be a factor effecting efficacy due to FDA recommending mineral oil being used in the control arm.

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

Comments on the ACD:

- Appraisal consultation comments

Cardiovascular risk reduction remains a major public health issue and an important component of which is optimising lipid management. Whilst statins are by and large effective from this point of view a residual risk remains (Particularly in

individuals with Diabetes). Being of South Asian origin myself I am aware that my personal lipid profile has a component of hypertriglycaremia. Having reviewed the trial evidence published in NEJM paper on Icosapent ethyl in addition to statin, I strongly recommend its widespread use to reduce the residual cardiovascular risk.

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

Yes

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

No.

With respect to clinical effectiveness, the decision to reject the clinical benefit demonstrated in the REDUCE-IT trial because the trial included a mineral oil-treated comparator group in not scientifically justified. As the committee acknowledges, the scientific literature demonstrates inconsistent effects of mineral oil treatment on lipid parameters and inflammatory markers. Many studies of cardiovascular risk reduction demonstrate a modest increase in LDL-cholesterol levels in statin-treated arms. The clinical scenario studied in REDUCE-IT, in which patients were enrolled with well-treated LDL cholesterol levels but elevated triglycerides, is common in clinical practice. It is inappropriate scientifically for NICE to largely base its decision not to recommend Icosapent ethyl in this group on its interpretation of what is essentially a questionable influence of mineral oil treatment in the comparator group.

The committee's decision that Icosapent ethyl should not be supported because the participants recruited to the REDUCE-IT trial differed from the population covered by NHS England is also not clinically justified. If this argument were to be followed, many clinical trials in the cardiovascular research field would be dismissed. The logical conclusion of the committee's comments here is that only trials conducted in England can reasonably be used to inform NICE decisions. This is obviously not the case - there are many examples in which medications have been recommended by NICE when the characteristics of the trial population or comparator treatments differed substantially from usual practice in England. Pertinent examples are in the field of anti-platelet therapy, in which the dose of aspirin administered in England differs from that studied in clinical trials; and geographical variation in clinical response was noted in the PLATO trial of ticagrelor. Reassuringly, there was no significant interaction according to ethnicity in REDUCE-IT which provides support that the findings are applicable to the population of England.
Whilst is acknowledged that 'optimal' therapy may evolve during the conduct of any clinical trial, that cannot be used as a cogent argument to dismiss findings of clinical benefit. There are many examples of drugs being recommended by NICE on the basis of clinical studies carried out before contemporary treatments have

been widely deployed (examples are the NICE recommendations for SGLT2 inhibitors in heart failure with reduced ejection fraction, when deployment of treatment with angiotensin-neprolysin inhibitors in the clinical trials could be argued to be low in relation to optimal contemporary practice).

The inclusion of the comment from the clinical advisor that "standard care in the NHS for diabetes includes SGLT2 inhibitors but it is uncertain how many people in REDUCE-IT had these treatments" is disingenuous, when NICE guidance on management of diabetes in adults (NG28) was only updated in February 2022 to recommend the positioning of SGLT2 inhibitors for cardiovascular risk reduction in type 2 diabetes.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are not sound for the reasons indicated in relation to the summaries of clinical effectiveness.

- 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?

No

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

REDUCE-IT is very strong and robust ‘safety outcomes data.’ Gives confidence.

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

Looks like there is a place for this. NICE needs to see what I can see: I can see it fitting into the 2022/23 DES and Outcomes Framework, especially considering our tasks to treat Ambulatory Care Sensitive Cases in 2022 and beyond. Icosapent Ethyl has a strong place and looks cost effective in reducing residual risks. It is making me rethink how I read Triglycerides as a bio-marker and something to act upon.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I would like to have the choice to prescribe this and look forward to a NICE TA for guidance.

- 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?

Please make it available for Secondary Care and Primary Care.

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

Comments on the ACD:

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I have reviewed the consultation document and looked at the trial data. I feel i am able to make comments.
I believe that patients have significant cardiovascular risk despite standard factors such LDL-C have been controlled.
Based on our current evidence I believe another modality for treatment would be useful and needed for these patients.

From the REDUCE-IT trial it has shown significant reduction in MACE alongside an acceptable tolerability profile.

I sincerely believe that icosapent ethyl would be a very much needed and useful addition.

Concerning suggestions that treatments effects are uncertain because of the mineral oil placebo I feel that this not born out of the data.

My view is aligned and supported by the modelling by the FDA and EMA.

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

Comments on the ACD:

- Appraisal consultation comments

Currently, Icosapent ethyl is licensed for use in patients with Tg > 1.7mmol/L while on statins in the setting of prior cardiovascular disease or have diabetes and one other CVS risk factor.

Using the above parameters, the number of eligible patients in UK will be significantly high.

What I would suggest NICE consider is a narrower eligibility using non-HDL cholesterol as an additional criteria rather than purely Triglycerides only.

Important to note that non-HDL-C (non-fasting sample of Total cholesterol - HDL cholesterol) is more reflective of atherogenicity in persons with elevated triglycerides. The constellation of increased triglycerides, reduced HDL-C, increased small dense LDL particles, and increased remnant cholesterol levels (primarily VLDL), is known as atherogenic type dyslipidaemia.

Instead of just using the cut off for Tg > 1.7mmol/L, we should target the highest risk group of patients and I would propose a Tg > 4.5mmol/L with a non-HDL cholesterol > 5.7mmol/L in the setting where the patient is already on maximum tolerated statins.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Icosapent ethyl for the treatment of hypertriglyceridaemia [ID3831] – ERG critique of ACD 2 response

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

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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.

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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.

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.

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

The ERG agrees that the use of PCSK9 inhibitors is not relevant to this appraisal as patients eligible for icosapent ethyl have LDL-C levels below 2.6 mmol/L, if patients in England and Wales are only eligible for PCSK9 inhibitors (alirocumab, evolocumab) when LDL-C levels are above 2.6 mmol/L.

3. *Icosapent ethyl's mechanism of action*

The ERG agrees with what the company seem to be asserting i.e., that uncertainty in the mechanism of action has little bearing on the interpretation of the results of an RCT per se. The uncertainty seems to arise because of the size of the treatment effect in REDUCE-IT compared to that in STRENGTH and the potential role of a placebo effect (see issue 4 below).

4. *Mineral oil placebo in REDUCE-IT and difference in results between the REDUCE-IT and STRENGTH trials*

No new evidence has been presented and so the critique by the ERG at technical engagement still applies.

5. *It is not appropriate to consider scenarios for an estimated reduction in treatment effect from 3% to 10%*

The company restate their argument presented in response to ACD 1 that a reduction in treatment effect due to the harmful effect of the mineral oil used as placebo suggested by the committee is implausible, in this case 3 to 10%, and that any plausible reduction should be no more than 3%. The ERG agrees with the company that the conclusion of the CHMP was that the maximum negative effect was 3%.[1] The company provide some additional evidence to support this in the form of Figures 5 to 8 based on what they report to be a replication of the FDA Cox proportional hazards regression to estimate the independent effect of LDL-C and CRP changes in the REDUCE-IT trial. The ERG can confirm that the maximum value of the change in HR, which is using the Hopkins method for estimating LDL-C, is 3%, which is based on a HR of 1.003 per unit change and trial observed change of 10 in LDL-C.[1] The ERG can also confirm that the report by the FDA did indicate that there was a plausible mechanism by which LDL-C increase might occur i.e., by reduction in the absorption of statins. This also matches the value estimated by Doi et al. 2021.[2] The FDA report also stated that: "the approximately 0.65 mg/L (50%) difference in hs-CRP between arms from baseline would increase the risk of cardiovascular outcomes by less than 0.3% in the placebo arm of the REDUCE-IT trial." (p. 54), although this was not cited as a mechanism of action of any placebo effect.[1] This contrasts with the value of 4% estimated by Doi et al. 2021 based on a 0.5 mg/L (50%) difference in arms. Therefore, the maximum, by a combination of all identified mechanisms including LDL-C and CRP, would seem to be about 3% based on the FDA analysis, but based on the Doi et al study, it would appear to be 7%. The major discrepancy between the two values seems to be the over 10-fold difference in the effect of CRP on cardiovascular disease risk. This prompted the ERG to conduct an informal web-search, by which a recent (2021) systematic review of reviews was found, which included 55 studies and reached the following conclusion:[3] "Following claims that CRP maybe be a novel CVD risk factor, it has been extensively studied in relation to an ever-increasing list of phenotypes and diseases, but it does not seem to be crucially relevant to any of them." (p. 31) It also cited a meta-analysis that showed that mortality was increased by CRP, but outcome was relative risk for highest vs. lowest CRP value, which is not translatable into

HR for number of mg difference. The ERG therefore consider that it remains plausible that there was a harmful placebo effect in the REDUCE-IT trial, although there is much remaining uncertainty as to the size of this effect.

6. ***A cross-validation model demonstrated the appropriateness of the company's model structure, showing that concerns raised in the ACD have minimal impact on clinical and economic outcomes***

No new evidence was presented by the company and so the critique by the ERG still applies.

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

No new evidence was presented by the company and so the critique by the ERG still applies.

8. ***There is no evidence to support a treatment waning effect in patients receiving icosapent ethyl***

No new evidence was presented by the company and so the critique by the ERG still applies.

9. ***Discrepancies between the original and updated cross-validations***

The company provided further explanation regarding the discrepancies between the original and updated cross-validations and the ERG is satisfied with the explanation and that the updated cross-validation comparison is likely appropriate.

10. ***Revised economic base case***

The ERG was able to approximately reproduce the company's updated base-case ICER: the ERG's ICER was £19,999 per QALY gained, and the discrepancy is likely caused by rounding of the new discounted price. The ERG base-case has been updated with the company's new price and the ERG performed several scenarios that may be useful to reflect the remaining uncertainty about the impact of treatment discontinuation (treatment waning) and a potential reduction in treatment effectiveness (Table 1).

Table 1: Cost-effectiveness analysis scenarios

Company base-case ACM2 (with new price)							
Icosapent Ethyl	[redacted]	11.587	[redacted]	[redacted]	0.385	[redacted]	£18.464
Placebo	[redacted]	11.201	[redacted]				
New company base-case (new price and 1.5% treatment effect reduction)							
Icosapent Ethyl	[redacted]	11.587	[redacted]	[redacted]	0.359	[redacted]	£19,999
Placebo	[redacted]	11.227	[redacted]				
ERG base-case: treatment waning upon treatment discontinuation at 10 years, no treatment effect reduction							
Icosapent Ethyl	[redacted]	11.526	[redacted]	[redacted]	0.325	[redacted]	£21,062
Placebo	[redacted]	11,.01	[redacted]				
Scenario 1: treatment waning upon treatment discontinuation at 5 years, no treatment effect reduction							
Icosapent Ethyl	[redacted]	11,479	[redacted]	[redacted]	0.278	[redacted]	£24,484
Placebo	[redacted]	11,201	[redacted]				
Scenario 2: company base-case with treatment effect reduction of 3%							
Icosapent Ethyl	[redacted]	11.587	[redacted]	[redacted]	0.333	[redacted]	£21,750
Placebo	[redacted]	11.254	[redacted]				
Scenario 3: ERG base-case but with treatment effect reduction of 3%							
Icosapent Ethyl	[redacted]	11.526	[redacted]	[redacted]	0.278	[redacted]	£24,821
Placebo	[redacted]	11.248	[redacted]				
Scenario 4: ERG base-case but with treatment effect reduction of 7%							
Icosapent Ethyl	[redacted]	11.526	[redacted]	[redacted]	0.216	[redacted]	£31,893
Placebo	[redacted]	11.310	[redacted]				
Scenario 5: treatment waning upon treatment discontinuation at 5 years with 7% treatment effect reduction							
Icosapent Ethyl	[redacted]	11.479	[redacted]	[redacted]	0.181	[redacted]	£37,019
Placebo	[redacted]	12.298	[redacted]				
Scenario 6: ERG base-case with treatment effect reduction of 1.5%							
Icosapent Ethyl	[redacted]	11.526	[redacted]	[redacted]	0.302	[redacted]	£22,817
Placebo	[redacted]	11.224	[redacted]				

Scenario 7: treatment waning upon treatment discontinuation at 5 years, treatment effect reduction 1.5%							
Icosapent Ethyl	[redacted]	11.479	[redacted]	[redacted]	0.257	[redacted]	£26,503
Placebo	[redacted]	11.222	[redacted]				
Scenario 8: treatment waning upon treatment discontinuation at 5 years, treatment effect reduction 3%							
Icosapent Ethyl	[redacted]	11.479	[redacted]	[redacted]	0.236	[redacted]	£28,816
Placebo	[redacted]	11.242	[redacted]				
Scenario 9: company base-case with treatment effect reduction of 7%							
Icosapent Ethyl	[redacted]	11.587	[redacted]	[redacted]	0.262	[redacted]	£27,900
Placebo	[redacted]	11.324	[redacted]				

References

[1] US Food and Drug Administration (FDA). November 14, 2019: Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting Announcement (FDA Briefing Document) [Internet]. Silver Spring, Maryland: FDA, 2019 [accessed 22.4.22] Available from: https://www.fda.gov/advisory-committees/november-14-2019-meeting-endocrinologic-and-metabolic-drugs-advisory-committee-meeting-announcement

[2] Doi T, Langsted A, Nordestgaard BG. A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs. Eur Heart J 2021;42(47):4807-17.

[3] Markozannes G, Koutsioumpa C, Cividini S, Monori G, Tsilidis KK, Kretsavos N, et al. Global assessment of C-reactive protein and health-related outcomes: an umbrella review of evidence from observational studies and Mendelian randomization studies. Eur J Epidemiol 2021;36(1):11-36.